ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2014 December 16; 6(12): 571-634

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

Contents

Monthly Volume 6 Number 12 December 16, 2014

World Journal of Gastrointestinal Endoscopy
Volume 6 Number 12 December 16, 2014

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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
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PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
December 16, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION
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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.v6.i12.571

World J Gastrointest Endosc 2014 December 16; 6(12): 571-583
ISSN 1948-5190 (online)

REVIEW

Quality indicators for colonoscopy: Current insights and caveats

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Received: August 26, 2014 Revised: September 21, 2014
Accepted: October 28, 2014
Published online: December 16, 2014

Abstract

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with removal of detected polyps has been shown to reduce the incidence and mortality of subsequent CRC. In many countries, population screening programs for CRC have been initiated, either by selection of patients for colonoscopy with fecal occult blood testing or by offering colonoscopy directly to average-risk individuals. Several endoscopy societies have formulated quality indicators for colonoscopy. These quality indicators are almost always incorporated as process indicators, rather than outcome measures. This review focuses on the quality indicators bowel preparation, cecal intubation rate, withdrawal time, adenoma detection rate, patient comfort, sedation and complication rate, and discusses the scientific evidence supporting them, as well as their potential shortcomings and issues that need to be addressed. For instance, there is still no clear and generally accepted definition of adequate bowel preparation, no robust scientific evidence is available supporting a cecal intubation rate ⩾ 90% and the association between withdrawal time and occurrence of interval cancers has not been clarified. Adenoma detection rate is currently the only quality indicator that has been shown to be associated with interval colorectal cancer, but as an indicator it does not differentiate between subjects with one or more adenoma detected.

Key words: Colonoscopy; Quality indicators; Bowel preparation; Cecal intubation; Withdrawal time; Adenoma detection rate; Screening; Complication; Interval colorectal cancer; Post-colonoscopy colorectal cancer

Core tip: Many endoscopy societies have formulated guidelines on quality indicators for colonoscopy, including bowel preparation, cecal intubation rate, withdrawal time and adenoma detection rate. These are mostly consensus-based process indicators, rather than outcome measures. The scientific evidence on which they are based is limited. Adenoma detection rate is currently the only quality indicator that has been shown to be directly associated with interval colorectal cancer, but also has its shortcomings.

Pullens HJM, Siersema PD. Quality indicators for colonoscopy: Current insights and caveats. *World J Gastrointest Endosc* 2014; 6(12): 571-583 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/571.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.571

INTRODUCTION

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to

the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with polypectomy has been shown to reduce both the incidence and mortality of subsequent CRC[1,2].

However, despite being the gold standard, colonoscopy is also known to be not a perfect test. From back-to-back colonoscopy studies, it is estimated that up to 25% of polyps are missed during colonoscopy[3,4]. Furthermore, the preventive effect of colonoscopy is most prominent for distal CRCs, whereas its role in preventing proximal CRCs is less evident[5,6]. Finally, up to 8% of CRCs occur within 3 years after a previous colonoscopy[7-12]. Despite technical advancements and increased professional awareness, this miss rate has not decreased over time[12]. Moreover, recent studies have shown that these so-called post-colonoscopy CRCs are most likely due to missed lesions, rather than being completely new lesions[13,14].

The incidence of CRC is steadily rising in many parts of the world[15]. Many countries have initiated population screening programs for CRC, either through selection of patients for colonoscopy with fecal occult blood testing (FOBT) or by offering colonoscopy directly to average-risk individuals[16,17]. This has resulted in an increase in the number of colonoscopies performed. For these mass screening programs to be successful, it is of utmost importance that colonoscopies are of high quality and performed according to the latest state of knowledge.

In an effort to optimize general performance of colonoscopy and to decrease inter-individual variation between physicians performing colonoscopy, several quality indicators have been suggested in recent years[18]. These quality indicators however all are process indicators rather than indicators of outcome. Ideally, the quality of colonoscopy should be measured by clinical outcome measures. The goal of colonoscopy in most cases is the detection of neoplastic lesions. After removal of premalignant neoplastic lesions, patients enter a surveillance program. The rate of the occurrence of interval cancers or post-colonoscopy CRCs, defined as CRCs diagnosed in the period between the last colonoscopy and the scheduled surveillance colonoscopy, is a more direct and probably better reflection of the quality of the colonoscopy performed than the main current quality indicators proposed in guidelines.

In this review, we will discuss the main current quality indicators for colonoscopy, the scientific evidence supporting them, as well as their potential shortcomings and issues that still need to be addressed.

BOWEL PREPARATION

A quality indicator issued by several international guidelines is that the endoscopist should report the quality of the bowel preparation for each colonoscopy[18,19]. Several guidelines state that ≥ 90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate[19,20]. The quality of bowel cleansing has been shown to impact the ability and time needed to reach the cecum and the detection of polyps, both small and large (≥ 10 mm)[21,22].

There are several bowel preparation medications available and regimens used for bowel preparation before colonoscopy. These vary from polyethylene glycol (PEG) based solutions, osmotic laxatives (sodium phosphate, magnesium citrate, sodium sulphate) or stimulant laxatives (senna, bisacodyl, sodium picosulphate), either alone or in combination.

In a meta-analysis of randomized controlled trials, split dose bowel preparation before colonoscopy has been demonstrated to significantly improve the number of satisfactory bowel preparations, and is associated with increased patient compliance and decreased nausea compared with full-dose PEG[23]. In a systematic review and meta-analysis, Enestvedt *et al*[24] concluded that bowel preparation with 4 liter of split dose PEG-solution is superior than other bowel preparation methods. Several endoscopy societies now recommend 4 liter split dose PEG-solution as the first choice bowel preparation[25], although 2 liter PEG-solution with ascorbate may be an alternative in the non-constipated patient. Routine use of sodium phosphate preparations is not recommended because of safety concerns, especially in patients with renal insufficiency[25]. In patients using PEG-solutions, the interval between the last ingested dose of PEG-solution and the colonoscopy should be 3-5 h, as this has been shown to result in significantly better bowel preparation[26,27].

In the literature, several risk factors for inadequate bowel preparation have been identified. Increasing age[28-31] and male gender[29-32] have repeatedly been reported. A medical history of colorectal surgery[28,29], diabetes[28,29] and cirrhosis[29,32], as well as inpatient status[30,32] have also been identified as risk factors for inadequate bowel preparation in several studies. Other risk factors that have been suggested in the literature are a procedural indication of constipation, a reported failure to successfully complete the bowel lavage, the use of tricyclic antidepressants, a history of stroke or dementia[32], a history of Parkinson's disease, being overweight, having had a positive FOBT[29], a history of hysterectomy[28] and being of African-American descent[31]. A history of previous polypectomy was a negative predictive factor for inadequate bowel preparation in the study by Ness *et al*[32]. Furthermore, a later colonoscopy starting time during the day[30-32] was associated with inadequate bowel preparation in several studies. Most of these studies however were conducted before the wide application of a split-dose bowel preparation regimen. Whether this association currently still is valid remains to be elucidated.

Several scales have been developed to standardize the reporting of bowel preparation quality. Aronchick *et al*[33] were the first to propose a validated bowel preparation scale. This is a 5 point categorical scale, rating bowel preparation as excellent (small volume of clear liquid; >

95% of surface seen), good (large volume of clear liquid covering 5%-25% of surface; > 90% of surface see), fair (some semi-solid stool suctioned or washed away; > 90% of surface seen), poor (semi-solid stool that could not be suctioned or washed away; < 90% of surface seen) or inadequate (repeat bowel preparation necessary). Unfortunately, the reliability of this scale for the distal colon is rather poor.

Rostom and Jolicoeur developed and prospectively validated another bowel preparation scale, the Ottawa scale[34]. In this scale, the colon is divided into three segments: right colon (cecum and ascending colon), mid colon (transverse and descending colon) and rectosigmoid. For each segment, bowel preparation is qualified using a 4 point scale (0: perfectly clear to 4: solid stools and lots of fluid) for each colon segment individually and a 0 to 2 fluid quantity rating as a global value for the entire colon. The scale thus has a range from 0 (perfect bowel preparation) to 14 (completely unprepared).

Finally, in 2009 Lai *et al*[35] introduced the Boston Bowel Preparation Scale (BBPS). In this validated bowel preparation scale, the colon is divided into the right colon (cecum and ascending colon), transverse colon (including both the hepatic and splenic flexure) and the left colon (descending colon and rectosigmoid). The BBPS is a ten point scale (0-9) with 0-3 points allocated to each colon segment, *i.e.,* 0 (unprepared colon segment that cannot be cleared), 1 (portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid), 2 (minor residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well) 3 (entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid). In the validation study, a score of $\geqslant 5$ was considered adequate.The BBPS differs from other preparation scales in that the score is applied after the endoscopist has performed cleansing maneuvers, like suctioning and washing.

All these scales have mainly been used in studies comparing new formulas or different schemes for bowel preparation[33,36-40], rather than being used to assist in clinical decision making. In a recent retrospective study, Calderwood *et al*[41] reported that the BBPS correlated with endoscopist behavior with regard to the advice for follow-up intervals for colonoscopy. A total BBPS score of $\geqslant 6$ and/or all segment scores $\geqslant 2$ provided a standardized definition of an "adequate" bowel preparation, whereas in 96% of examinations with a total score of $\leqslant 2$ a repeat examination within 1 year was recommended. For scores 3 to 5 however, recommended surveillance intervals varied widely between endoscopists. Future studies should focus on prospectively evaluating these cut-offs for surveillance interval recommendations and ideally associating them with relevant clinical outcome measures.

The widely adopted quality indicator for bowel preparation has several shortcomings. First of all, there is still no clear and generally accepted definition of adequate bowel preparation. Furthermore, the mere reporting of the quality of bowel preparation in itself is unlikely to significantly affect the quality of the colonoscopies performed, unless it becomes more clear what bowel preparation quality is the absolute minimum to detect relevant findings and to prevent interval cancers. There is also no clear policy on how to proceed when a patient's bowel is inadequately cleansed; the only relevant published studies on this topic had either small patient numbers[42] or a retrospective design[43].

The rule that $\geqslant 90\%$ of patients undergoing colonoscopy should have an excellent or adequate bowel preparation is consensus based and has found its way into several guidelines[19,20]. However, there is no scientific evidence to support this cut-off at 90%. Although inadequate bowel preparation has been shown to negatively affect the rate of detected polyps, this does not appear to be the case for CRCs[21]. It is conceivable that, through the negative effect on the detection of adenomas, an inadequate bowel preparation is associated with a higher rate of interval cancers, but to date, there is no direct evidence to support this.

CECAL INTUBATION RATE

In order to visualize the entire colonic mucosa, intubation of the endoscope to the cecum is mandatory. Cecal intubation is defined as introduction of tip of the colonoscope into the cecal pole, proximal of the ileocecal valve in order to have the entire cecum visualized. Although this sometimes may be challenging, there is consensus that each endoscopist should have a cecal intubation rate of $\geqslant 90\%$ of all cases[18-20,44,45]. When not taking into account obstructing CRCs, inadequate bowel preparation or severe colitis, this adjusted cecal intubation rate should be $\geqslant 95\%$[18]. Also, in $\geqslant 95\%$ of all screening colonoscopies the cecum should be intubated[18,19]. Furthermore, cecal intubation should be documented by naming and photographing the landmarks of the cecum, *i.e.,* the appendiceal orifice, the ileocecal valve and/or the terminal ileum.

In the literature, several factors have been associated with a higher risk of incomplete colonoscopy or more difficult intubation, with female gender being the most frequently reported predictive factor[46-50]. In addition, patients with advanced age[46,49,50] or a low body mass index[48-50], or in women with a history of hysterectomy[47] or diverticular disease[50], colonoscopy is reported to be more difficult and more often incomplete. Finally, poor bowel preparation and lower endoscopist annual case volume have been reported to be associated with a higher risk of incomplete colonoscopy[49].

Completeness of the colonoscopy is associated with a reduction in mortality from CRC[6]. In a study by Neerincx *et al*[51], a secondary colonoscopy after previous incomplete colonoscopy yielded initially missed advanced

neoplasia (CRC or advanced adenoma) in 4.3% of patients. In a study on the yield of CT-colonography after incomplete colonoscopy in 136 patients, in 13.9% of patients one or more additional colonic neoplastic lesions (polyp(s) and/or CRC) were found[52].

These findings suggest that in cases of incomplete colonoscopy the clinician should always perform additional imaging to visualize the remaining colon. Following incomplete colonoscopy, the cecum can usually be intubated in the majority of patients during a repeat colonoscopy with readily available endoscopic instruments, suggesting that a repeat colonoscopy should always be considered[47,53]. CT-colonography might be a useful alternative in these cases, with the additional benefit of detecting potentially relevant extra-colonic findings[52].

It is important to keep in mind that there is no robust scientific evidence for a cecal intubation rate of $\geqslant$ 90%. Although it is obvious that an endoscopist is not able to adequately inspect colon segments that were not intubated, the accepted minimal cecal intubation rate is based on consensus rather than on a scientific basis.

WITHDRAWAL TIME

In 2006, Barclay *et al*[54] were the first to report that colonoscopists with a mean withdrawal time of 6 minutes or more had higher detection rates of any neoplasia and advanced neoplasia. Since then, a recommended mean withdrawal time of at least 6 min has been formulated as a quality indicator in several colonoscopy guidelines[18-20].

However, colonoscopic withdrawal time as a quality indicator is not undisputed. Since the initial publication by Barclay *et al*[54], several observational studies have reported on the association between colonoscopic withdrawal time and the number of detected polyps[55-59]. Other large studies could however not confirm these findings[60-62]. Furthermore, interventions directed at optimizing withdrawal time, in an attempt to improve polyp detection, have yielded conflicting results. Although Barclay *et al*[63] did report higher rates of overall and advanced neoplasia detection during screening colonoscopy after implementing a time-dependent colonoscopic withdrawal protocol, other authors were not able to find a difference in overall polyp detection rate after formally implementing such a policy[64,65].

Gellad *et al*[66] were the first to study the association between withdrawal time during an initial, negative colonoscopy and the risk of developing neoplasia in the next five years. They did not detect any significant association. However, mean baseline withdrawal time in the 13 participating centers was rather long (greater than 12 min), possibly explaining the non-confirmatory results. It is possible that withdrawal time no longer is an adequate quality measure for screening colonoscopy above a certain threshold.

The use of the indicator withdrawal time is based on the assumption that endoscopists who take longer to withdraw the colonoscope also use specific techniques to improve visualization of the entire colonic mucosa. A study of two endoscopists with different rates of missed adenomas indeed showed that a better quality colonoscopic withdrawal technique was associated with a longer withdrawal time[67]. Lee *et al*[62] reported that the number of detected adenomas was found to be associated with the quality of withdrawal technique, but not necessarily related to withdrawal time. Withdrawal technique may therefore be a more important indicator for colonoscopy quality than withdrawal time. At present, there is however no generally accepted way to quantify an optimal withdrawal technique.

It is conceivable that the derived quality indicator withdrawal time in the future will be replaced by a measure of the proportion of the colonic mucosa that is adequately visualized during colonoscopy. Interestingly, Hong *et al*[68] recently reported on a fully automated three-dimensional reconstruction technique from individual colonoscopy images. Such a technique might eventually give real time feedback to the endoscopist on areas of the colonic wall that are not adequately inspected, thus enabling revisiting these areas during the same procedure. The percentage of the colon surface that is visualized by the endoscopist may potentially serve as a new quality indicator for colonoscopy. Furthermore, information on inspected and uninspected areas of the colonic wall may help in training endoscopists, giving insight in possible "blind spots" during scope withdrawal.

As mentioned above, the association between the quality indicator withdrawal time and the occurrence of interval cancers has not yet been elucidated.

ADENOMA DETECTION RATE

The adenoma detection rate (ADR) is defined as the proportion of screened subjects in whom at least one adenomatous lesion is identified[18,19,69]. In an asymptomatic screening population, an ADR of $\geqslant$ 25% in men and of $\geqslant$ 15% in women over 50 years old has been proposed in the American screening guidelines[18], whereas the British Quality Assurance Guidelines for Colonoscopy has set the standard ADR, based on their own pilot data, at $\geqslant$ 35% of all screening colonoscopies in patients who had a positive FOBT[19].

Repeatedly, considerable variations between endoscopists in the rate of detected polyps and adenomas have been shown[70-74]. The ADR is the only current quality indicator that has been demonstrated to be directly associated with interval colorectal cancer. In the landmark study by Kaminski *et al*[69], an ADR $\geqslant$ 20% was associated with a reduction in interval colorectal cancers. A recent study by Corley *et al*[75] showed that the ADR was inversely associated with the risk of interval CRC, but also with advanced-stage interval cancers and fatal interval cancers.

In line with these findings, many recent studies have focused on ways to optimize adenoma detection, ranging from inexpensive and easy to implement interventions in

Figure 1 Third-Eye retroscope.

daily clinical practice, to minor adaptations of currently used colonoscopy equipment to completely new colonoscopy platforms.

Position changes during colonoscope withdrawal have been reported to increase luminal distension and may reduce the rate of missed lesions[76]. Two small randomized studies have indeed suggested that dynamic patient position changes may improve polyp detection[77,78], but there was no difference in polyp or adenoma detection rates in another, larger randomized study[79].

Endoscopy nurse participation as a second observer during colonoscopy has been reported to significantly increase the overall number of detected polyps and adenomas found during colonoscopy[80], and appears an easy to implement intervention to increase polyp detection rate (PDR) and ADR[81].

Furthermore, the time of performing the colonoscopy may have an effect on the ADR. Testing the hypothesis that fatigue of the endoscopist, which increases as the day progresses, might affect ADR, Sanaka *et al*[82] were the first to report that the ADR of endoscopists was significantly higher in morning colonoscopies than in afternoon colonoscopies. The time of the colonoscopy during the day was an independent predictor for adenoma detection. These findings have been confirmed by almost all other studies on this subject[83-86]. Gurudu *et al*[83] proposed that colonoscopies should best be performed in half-day blocks by different physicians. They found no significant difference in ADR between morning and afternoon colonoscopies when endoscopists only perform colonoscopies in half-day blocks.

The use of high definition colonoscopy as compared to standard video colonoscopy has been reported to have only a marginal beneficial effect on the detection of colonic polyps and adenomas in a recent meta-analysis[87]. Due to heterogeneity of the included studies and the fact that no randomized trials were available, these results should be interpreted with some caution.

Virtual chromoendoscopy consists of multiple techniques that use a narrow spectrum of wavelengths with a decreased penetration depth to enhance visualization. Light of short wavelengths increases vascular contrast of the mucosa, potentially improving visualization and the identification of neoplastic lesions. Although there are some conflicting data, most studies and meta-analyses have not been able to demonstrate a substantial increase in ADRs with pan-colonic virtual chromoendoscopy[88-90].

Cap-assisted colonoscopy is performed by attaching a transparant cap to the tip of the colonoscope. These caps were originally designed to be used during endoscopic mucosa resection, but they might also aid in depressing colonic folds to improve visualization of the entire colonic mucosa. However, in a meta-analysis of 16 randomized controlled trials including 8991 subjects, Ng *et al*[91] concluded that cap-assisted colonoscopy only had a limited effect on ADR, although a higher proportion of patients with polyp(s) were detected when a cap was attached (relative risk 1.08; 95%CI: 1.00-1.17).

It has been reported that retroflexion of the colonoscope might aid in the removal of polyps that are difficult to access endoscopically[92,93]. Conceivably, inspection with a retroflexed colonoscope may also help in increasing visualization of the proximal aspects of colonic folds, especially in the right colon, and thereby increasing ADR. However, although this technique appears safe in experienced hands, both a randomized study and a large prospective observational study failed to demonstrate a relevant increase in the number of detected polyps[94,95].

In recent years, several new devices have been developed to improve visualization of the proximal sides of colonic folds and inner curvatures. First, the Third-Eye Retroscope® (Avantis Medical Systems, Inc) is a through-the-scope catheter with a camera and light source at the tip. After advancement through the working channel of the colonoscope, the catheter is retroflexed 180° (Figure 1). It then provides a 135° retrograde view of the colon. In a randomized, multicenter back-to-back study, the Third-Eye Retroscope yielded a net additional detection rate of 29.8% for polyps and 23.2% for adenomas compared to standard colonoscopy[96]. An advantage of this device is that it can be used with standard colonoscopy equipment. However, use of this device in clinical practice may be hampered by the fact that the Third-Eye Retroscope needs to be removed from the working channel in case a polypectomy snare or biopsy forceps is used. Furthermore, when the device is in place, the colonoscope has reduced suctioning capacity. These factors may increase procedural time and may be experienced as bothersome by the endoscopist.

Recently, Gralnek *et al*[97] reported the results of the first international, multicenter, randomized, back-to-back study with the new Full Spectrum Endoscopy™ platform (FUSE; EndoChoice®, Alpharetta, Georgia, United States). The full spectrum colonoscope allows a high resolution 330° view of the colonic lumen, as compared to the 140°-170° of standard colonoscopes (Figure 2). In their study including 185 subjects, the adenoma miss rate

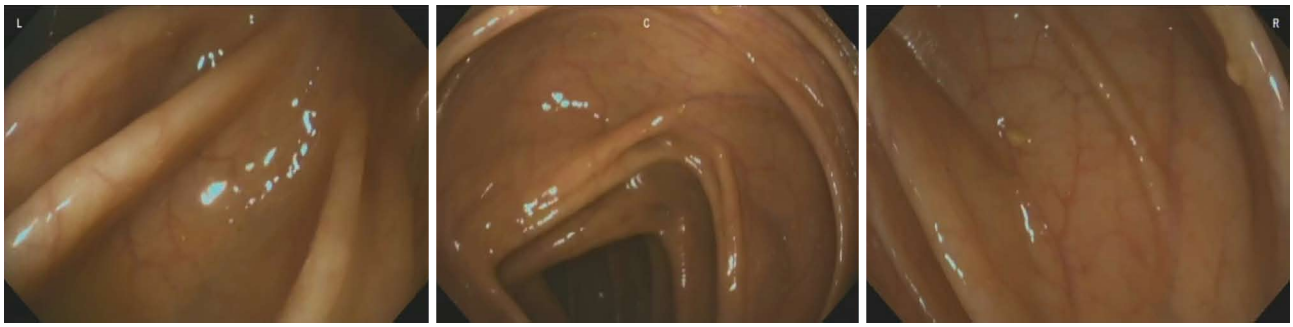

Figure 2 Endoscopic view using the Full Spectrum Endoscopy™ platform.

was significantly lower in patients in whom colonoscopy was performed with the full-spectrum endoscope first: in the latter group five (7%) of 67 adenomas were missed *vs* 20 (41%) of 49 adenomas in the group that underwent standard colonoscopy first ($P < 0.0001$). Although these results seem promising, further studies are required to determine the potential role for this system in non-expert centers. The obvious disadvantage in the implementation of this new device in daily clinical practice, is that new colonoscopes and main control units are required.

A potential downside of the current definition of ADR is that it does not discriminate between subjects in whom the endoscopist detects one *vs* more than one adenoma. It has been shown that physicians are more likely to miss additional adenomas during colonoscopy, when they have already detected two or more[4].

Wang *et al*[98] concluded that, despite comparable and adequate ADRs, there can be considerable variability between endoscopists with regard to the total number of adenomas detected per colonoscopy. They introduced a metric called the ADR-plus, the mean number of incremental adenomas after the first, and by coupling this to the ADR the authors were better able to distinguish high- from low-performing endoscopists. Lee *et al*[99] introduced two new measures in addition to the ADR that also may provide additional information on the inter-individual variation in the quality of performing colonoscopy: mean adenomas per procedure (MAP) and mean adenomas per positive procedure (MAP+). However, how these new metrics translate to the occurrence of interval cancers is currently not known.

PATIENT COMFORT AND SEDATION

Several guidelines recommend that sedation dosages as well as patient comfort scores should routinely be reported and monitored[19,20]. In their position statement on quality in screening colonoscopy, the European Society of Gastrointestinal Endoscopy proposed that no more than 1% of patients should have a saturation below 85% for more than 30 s or should require administration of a reversal agent[20].

Patient comfort in the screening setting is important, as patients who consider screening colonoscopy as being too uncomfortable, are less likely to participate[100]. It may obviously impact the effect of population screening when a significant proportion of the target population does not participate. Recently, Rostom *et al*[101] have prospectively validated a nurse-assisted patient comfort score in a multicenter, international setting, allowing for a uniform registration of patient comfort and comparison of colonoscopy practices. The various endoscopic societies have not yet adopted this validated comfort score. Which scores are considered acceptable and how to avoid drop-outs from the screening program has yet to be determined. Measuring comfort has the obvious caveat that endoscopists, nurses and patients may have different opinions about the level of (dis)comfort during the procedure.

Discomfort during colonoscopy can be reduced by the administration of sedatives. There is worldwide a large variation in the use of sedation for colonoscopy[102-105]. In some countries the majority of patients undergo colonoscopy unsedated, while elsewhere sedation with benzodiazepines combined with opiates is the standard of care. Entonox (nitrous oxide and oxygen) is frequently used in some countries, while elsewhere propofol and general anesthesia are increasingly being used in daily practice. Severe sedation-related complications have been reported to be rare: Behrens *et al*[106] reported a rate of 0.01% in their study of 388404 endoscopies. However, sedation-related adverse events need to be prevented, especially in an otherwise healthy screening population. There is however no validated score to record the level of sedation during colonoscopy, nor is there an accepted gold standard regarding sedation for colonoscopy.

Interestingly, a recent study from the United Kingdom screening program shows that, although there are wide variations in the use of sedation, colonoscopists' individual medication practice does not appear to be related to the occurrence of significant discomfort[102]. Instead, it is suggested that the best endoscopists cause less patient discomfort while using less sedation[103].

COMPLICATION RATE

Colonoscopy is an invasive procedure that inadvertently will lead to complications in a small subset of patients. The rate of complications obviously is not necessarily associated with the interval CRCs. However, for a

Table 1 Quality indicators and their shortcomings

Quality indicator	Proposed standard	Unresolved issues
Bowel preparation	Each endoscopy report should state the quality of the bowel preparation[18,19] ⩾ 90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate[19,20]	No evidence to support a cut-off of ⩾ 90% No clear and generally accepted definition of adequate bowel preparation Unclear what bowel preparation quality is the absolute minimum to detect relevant findings and prevent interval cancers No clear policy on how to proceed in case of inadequate bowel preparation
Cecal intubation rate	Overall cecal intubation rate of ⩾ 90%[18-20] Adjusted cecal intubation rate of ⩾ 95%[18,19] Cecal intubation rate of ⩾ 95% in all screening colonoscopies[18,19]	No robust scientific evidence to support a cut-off of ⩾ 90% No evidence supporting an association between cecal intubation rate and the occurrence of interval CRC
Withdrawal time	⩾ 6 min on withdrawal from cecal pole to anus[18-20]	Conflicting reports on the association between withdrawal time and the number of detected polyps Interventions directed at optimizing withdrawal time have yielded conflicting results No evidence supporting an association between withdrawal time and the occurrence of interval CRC Better endoscopic withdrawal technique is not necessarily associated with withdrawal time An indirect measure to quantify the proportion of the colonic mucosa that is adequately visualized
Adenoma detection rate	⩾ 25% in men and ⩾ 15% in women over 50 yr[18] ⩾ 35% of all screening colonoscopies in patients with a positive fecal occult blood testing[19]	The only quality indicator that has been shown to be directly associated with interval CRC Does not discriminate between subjects in whom the endoscopist detects one *vs* more than one adenoma Does not optimally differentiate between high- and low-performing endoscopists
Patient comfort and sedation	Routinely reporting and monitoring of patient comfort scores and sedation dosages[19,20]	Until recently no validated patient comfort score was available Not yet clear what patient comfort scores are considered acceptable The endoscopist, the nurse and the patient may have different opinions about the level of comfort during the procedure No gold standard regarding sedation during colonoscopy No validated score to assess the level of sedation during colonoscopy
Complication rate	Perforation in < 1:1000 colonoscopies[18-20] Post-polypectomy bleeding in < 1:100 colonoscopies with polypectomy[18,19]	Consensus based Complication rate is mainly dependent on the number of therapeutic colonoscopies, which may vary between screening strategies (colonoscopic screening of the entire population *vs* selection of high-risk individuals through fecal occult blood testing)

CRC: Colorectal cancer.

population screening program to have an overall beneficial effect, it is crucial that complication rates are low.

Perforation is the most serious complication of colonoscopy. It is defined as the presence of air, luminal contents or instrumentation outside the gastrointestinal tract[19]. It may result from mechanical trauma to the bowel wall, overinsufflation of the colon, or as a result of a therapeutic procedure. In the literature, reported overall rates of perforation range from 0.1%-0.6%[107-109]. The perforation rate for diagnostic colonoscopies is lower than that of therapeutic interventions. The British guidelines for screening colonoscopy state a standard of < 1:1000 risk of perforation in all colonoscopies[19,20], and a < 1:500 risk of perforation in colonoscopies in which polypectomy is performed[19]. This is largely consistent with the American guidelines[18], although it is important to keep in mind that there may be a significant variation in perforation risk between a screening population in which each participant undergoes a colonoscopy and a screening population that is pre-selected by means of fecal occult blood testing. Proportionally, it can be expected that more polypectomies will be performed in the latter. Each country should set its own standards according to the local screening strategy.

Historically, surgical closure or resection of the perforated colon segment was the only therapeutic option in case of iatrogenic colonic perforation. Several case series have reported on successful endoscopic closure of small iatrogenic bowel wall defects using metallic endoclips, either with endoclips alone or using a combined technique of endoclips and endoloops[110,111]. In recent years, the over-the-scope clip (Ovesco Endoscopy GmbH, Tuebingen, Germany) has become available, with high rates of successful perforation closure in the first reported case series[112,113].

Bleeding is the most common complication after polypectomy. Based on the literature, several guidelines set a standard of post-polypectomy bleeding in < 1:100 colonoscopies with polypectomy[18,19]. It is known that the risk of bleeding increases with size of the lesion and a more proximal location in the colon[114]. Several endoscopic techniques can be used to prevent bleeding. Cold snaring of small, non-pedunculated polyps may prevent delayed bleeding[115], even in anticoagulated patients[116]. Submucosal injection with saline and epinephrin prevents immediate bleeding but probably not delayed bleeding[117]. Furthermore, prophylactic placement

Table 2 Potential measures to improve performance per quality indicator

Quality indicator	Potential intervention to improve performance	Strength of scientific evidence
Bowel preparation	Split dose bowel preparation	Meta-analysis of randomized controlled trials
	Last ingested dose of PEG-solution 3-5 h before colonoscopy	Observational, prospective studies
Cecal intubation rate	Additional training and use of auxiliary endoscopic instruments (*e.g.*, pediatric colonoscope)	Expert opinion
Adenoma detection rate	Endoscopy nurse participation as a second observer	Randomized, multicenter studies
	Perform colonoscopy in the morning or in half-day blocks	Retrospective studies
	High definition colonoscopy (compared to standard video colonoscopy, marginal effect)	Meta-analysis
	Cap-assisted colonoscopy (marginal effect)	Meta-analysis of randomized controlled trials
	Third-Eye Retroscope	Randomized, multicenter study
	Full Spectrum Endoscopy	Randomized, multicenter study
Complication rate	Cold snaring of small, non-pedunculated polyps may prevent bleeding	Prospective, multicenter, observational study and small single center randomized controlled study
	Submucosal injection with saline and epinephrin prevents immediate bleeding	Randomized study
	Prophylactic placement of a detachable snare around the stalk of a pedunculated polyp prevents bleeding	Randomized studies
	Prophylactic closure of the polypectomy site with metallic clips after removal of large (> 2 cm) sessile or flat lesions may prevent bleeding	Retrospective study

of a detachable snare around the stalk of a pedunculated polyp may prevent bleeding[118,119], as well as prophylactic closure of the polypectomy site with metallic clips after removal of large (> 2 cm) sessile or flat lesions[120].

Post-polypectomy coagulation syndrome (PPCS), or transmural burn syndrome, is a known complication of colonoscopic polypectomy. It is defined by the development of abdominal pain, fever, leukocytosis and peritoneal inflammation in the absence of frank perforation that occurs after polypectomy with electrocoagulation[121]. To our knowledge, there is only one study that specifically focused on PPCS. In this large retrospective study, its incidence is reported to be 0.07% of all colonoscopies with polypectomy. Hypertension, a lesion size $\geqslant$ 10 mm and non-polypoid configuration of the lesion were independently associated with PPCS[121]. Correct identification of this entity is important, as this may avoid unnecessary explorative laparotomy. PPCS can usually be treated medically without a need for surgical intervention and without mortality. PPCS is not yet included in the current guidelines.

CONCLUSION

In summary, the main quality indicators for colonoscopy all have their shortcomings (Table 1). Most of these have been formulated based on consensus. Following the guideline Quality Indicators for Colonoscopy from the American Society of Gastrointestinal Endoscopy from 2006[18], many other countries have adopted these same quality indicators. The scientific evidence on which they are based is however limited. Potential measures to improve performance on individual quality indicators are summarized in Table 2.

What is not yet clear is how to proceed when a fellow or senior endoscopist does not meet the required standards. Individualized additional training or a binding negative advice to continue the fellowship could be an option for endoscopists in training. However, this could be difficult for senior endoscopists that have practiced for years, especially when the scientific basis for these quality indicators is still not well established. What further needs to be addressed, is how to check that endoscopists indeed perform colonoscopy according to the standard of care set by their peers or national guidelines.

ADR currently is the only quality indicator that has been shown to be directly associated with the outcome measure interval colorectal cancer. As such, it seems reasonable to let this indicator prevail in discussions with endoscopists who fail to meet the set standards.

Ideally, endoscopists should only be evaluated and compared by the most relevant outcome measure in the context of screening colonoscopies, i.e. the occurrence of interval CRCs. Since the incidence of interval CRCs is fortunately rather low, and the duration between colonoscopy and interval CRC is rather long, this may prove to be too slow and rigid a quality indicator in daily practice to timely intervene in case of substandard colonoscopy performance.

Until we find a better measure to approximate the risk of interval CRCs, the current set of quality indicators will have to suffice. However, they need to be interpreted with caution and continuously adjusted as more information becomes available. For instance, both withdrawal time and ADR are a derivative of the quality with which the entire colonic mucosa is visualized during colonoscopy and in time may be replaced with a more direct measure for the proportion of the colonic mucosa that is inspected.

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P- Reviewer: Herszenyi L, Jonaitis L, Yao CL **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Zhang DN

World Journal of Gastrointestinal Endoscopy

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v6.i12.584

World J Gastrointest Endosc 2014 December 16; 6(12): 584-591
ISSN 1948-5190 (online)

MINIREVIEWS

Myths, fallacies and practical pearls in GI lab

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Received: August 25, 2014 Revised: October 7, 2014
Accepted: October 31, 2014
Published online: December 16, 2014

Abstract

Many prevalent practices and guidelines related to Gastrointestinal endoscopy and procedural sedation are at odds with the widely available scientific-physiological and clinical outcome data. In many institutions, strict policy of pre-procedural extended fasting is still rigorously enforced, despite no evidence of increased incidence of aspiration after recent oral intake prior to sedation. Supplemental oxygen administration in the setting of GI procedural sedation has been increasingly adopted as reported in the medical journals, despite clear evidence that supplemental oxygen blunts the usefulness of pulse oximetry in timely detection of sedation induced hypoventilation, leading to increased number of adverse cardiopulmonary outcomes. Use of Propofol by Gastroenterologist-Nurse team is erroneously considered dangerous and often prohibited in various institutions, at the same time worldwide reports of remarkable safety and patient satisfaction continue to be published, dating back more than a decade. Of patient monitoring practices that have been advocated to be standard, many merely add cost, not value. Advances in the technology often are not incorporated in a timely manner in guidelines or clinical practices, *e.g.*, Capsule endoscopy or electrocautery during GI procedures do not interfere with proper functioning of the current pacemakers or defibrillators. Orthopedic surgeons have continued to recommend prophylactic antibiotics for joint replacement patients prior to GI procedures, without any evidence of need. These myths are explored for a succint review to prompt a change in clinical practices and institutional policies.

Key words: Endoscopy gastrointestinal; Pulse oximetry; Oxygen supplemental; Propofol; Conscious sedation; Deep Sedation; Fasting preprocedural; Standards of Care; Clinical Practice Guidelines

Core tip: Many prevalent endoscopic procedural practices and policies are not only unsupported by clinical and scientific evidence, but are counterproductive. Rather than enhancing patient safety and comfort, these increase risk and expense, introduce unnecessary delays. Evidence to reach proper decisions about these topics has been available for a while, but is not appropriately acknowledged and implemented. Avoiding these pitfalls can have a significant positive impact because these policies cover routine events, actions and decisions, including: required prolonged pre-procedural fasting, routine supplemental oxygen during sedation, prohibition of Propofol use by non-anesthesia personnel, multiple monitoring practices and prophylactic recommendations.

Kumar P. Myths, fallacies and practical pearls in GI lab. *World J Gastrointest Endosc* 2014; 6(12): 584-591 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/584.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.584

MYTH

"The great enemy of the truth is very often not the lie-deliberate, contrived, and dishonest - but the myth - persistent, persuasive and unrealistic." - John F Kennedy.

A fallacy is a mistaken belief, based on flawed or incomplete data or an unsound argument. A fallacy,

once discredited, loses its force of persuasion, *e.g.,* the earth is flat. Without careful review of the key evidence contradicting a simplistic impression, someone new to a topic can easily come to an erroneous conclusion.

A Myth, on the other hand, is complex and tenacious. Despite conclusive refuting data and reasoning, myths can persist for an impressive period of time. In fact, some myths have resurgences and succeed in replacing established sound practices with erroneous ones.

History is replete with myths propounded by giants of their times.

Aristotle thought that while the heart was the seat of intelligence, the brain cooled the blood. He reasoned that humans are more rational than the beasts because, among other reasons, they have a larger brain to cool their hot-bloodedness!

Galen (second century), was one of the foremost physicians of his time. He deliberately engaged others in debate to prove them wrong. It is ironic that he made the practice of bloodletting a standard treatment that continued for more than a thousand years! That myth was responsible for more deaths from intervention than perhaps any other single medical procedure. On December 12, 1799, President George Washington developed a sore throat. As treatment, about three liters of his blood were removed from his body by venesection during a 10-16 h period (with his consent and at his request). He consequently died.

Modern medicine aspires to be evidence based, but there is a strong undercurrent of tradition and reverence for experts. Many of the clinical practices start as empirical attempts but then gain mythological flavor. Many guidelines are nothing more than intuitive opinions but are often rigidly enforced despite evidence indicative of lack of effectiveness or harm.

"Whatever is almost true is quite false, and among the most dangerous of errors, because being so near truth, it is more likely to lead astray." - Henry Ward Beecher.

In many GI labs around the world, the following myths and fallacies are currently believed and practiced, as reflected in the published articles, institutional policies and personal practice patterns. Their persistence serves as testament to the mythical and entrenched nature of these beliefs.

MYTH: PRIOR TO MODERATE SEDATION, OVERNIGHT FASTING IS EFFECTIVE AND ESSENTIAL FOR PREVENTION OF ASPIRATION

Prolonged pre-procedure fasting requirement, (regardless of the time of day when the procedure gets done) is a rigidly enforced "rule" in many institutions. Extensive review of literature has failed to show any statistical evidence of increased risk of aspiration despite recent oral intake, in relation to endoscopic and other moderate procedural sedation[1,2]. The myth of Nothing orally after midnight has persisted in many institutions.Some others have adopted an arbitrary 4-h fasting requirement. This frequently leads to delay and often inconveniences the patient. No research data has shown the value of even 2-h intake restriction[1,2].

The rationale provided is: (1) Oral intake leads to increased gastric content; (2) Gastric content is vomited during the sedation; and (3) Vomit is aspirated in the respiratory tract, creating a complication.

The clinically-observed facts are: Gastric content is not well correlated with recent intake[1], and may be low despite the intake or may be high despite fasting for extended duration, due to gastric retention. Endogenous gastric secretion and saliva add to it in variable amounts.

In the setting of GI bleeding, the stomach is often filled with blood and blood clots. People coming in with food bolus impactions and with a considerable amount of food in their stomachs have undergone emergency endoscopy without a high incidence of aspiration.

Vomiting and regurgitations are extremely rare during the endoscopic procedures under current procedural sedation and endoscopic techniques, even when significant gastric contents are present.

In the rare event of vomiting, aspiration is uncommon, partly because patients for endoscopic procedures are generally not in supine position, and many have some protective reflexes.

Stated differently: (1) Gastric contents: not well correlated with liquid intake after an hour or more; (2) Gastric contents: very low risk of vomiting; and (3) Vomiting: very low risk of aspiration.

Prohibition on chewing gum or similar extremely restrictive measures have no data or basis to support them.

A case can be made for usefulness of liberal clear liquid intake more than a couple of hours before the procedure: Proper hydration improves the patient's general well-being, helps avoid dehydration, and may make intravenous access easier.

The American Society of Emergency Physicians panel reviewed the scientific data and evidence related to pre-procedural sedation oral intake and made a policy change in 2005 to remove the requirement of fasting from moderate sedation, leaving the decision to the discretion of the treating physician[1].

Since then and until now, no increased incidence of aspiration-related complications has been observed or reported since then. After the more-recent follow-up review, the clinical policy was reaffirmed and kept unchanged[2].

Pearl

For diagnostic GI endoscopic procedures, it makes intuitive sense to instruct patients not to take solids immediately prior to Gastroscopy, as it will impair visualization. If for some reason this is not the case, then recent oral intake should not be considered an absolute contraindication. The oral intake status of

all patients should be reviewed and discussed with the patient, including the potential risk of aspiration even if the patient has been fasting. If, in the judgment of the treating physician, the benefits of the procedure far outweigh the potential risk of aspiration, and the patient consents and assumes the risk, then proceeding with the sedation and the procedure should be individualized and outcomes should be reviewed on an ongoing basis.

MYTH: PROCEDURAL SEDATION SHOULD INCLUDE ROUTINE ADMINISTRATION OF SUPPLEMENTAL OXYGEN TO INCREASE PATIENT SAFETY

Supplemental oxygen use is frequently (erroneously) advocated for procedural sedation in the GI lab. Often, its use is mandated by the institutional policy and is enforced for all patients.

However, those advocating this practice do not dispute the following: (1) When hemoglobin is near 100% saturated, additional fractional increase in the inspired oxygen cannot further increase oxygen content of the blood; (2) Pulse oximetry does not measure ventilation. It estimates oxygen saturation of hemoglobin. Alveolar ventilation serves the function of more than just oxygenation of the blood. CO_2 clearance from the lungs is the other major process; (3) There is a lag between onset of hypoventilation and development of hypoxemia as reflected by oxygen desaturation; and (4) The reason for the desaturation in this setting is not reduction in oxygen in the ambient environment, but due to the patient's hypoventilation induced by the sedative agents.

Oxygen supplementation is appropriate in the setting of low ambient oxygen: (1) Lack of oxygen in the ambient air; (2) Lower oxygen saturation; (3) oxygen supplementation; and (4) Improved oxygen saturation in the blood. High altitude physiological observations and studies have demonstrated that humans tolerate isolated very low oxygen saturation levels for short periods of time very well.

The myth of appropriateness of oxygen supplementation to treat hypoventilation-related desaturation is a fallacy because it does not take into account the etiology and pathophysiology of desaturation.

Pulse oximetry value is a proxy and an indirect indicator of alveolar ventilation, just as urine output is an indirect indicator of renal function. Instances of reduced urine output should not all be treated in the same way. Giving a diuretic to a dehydrated patient may temporarily increase the urine output, but it would be precisely the wrong thing to do.

Similarly, if supplemental oxygen is given, various ventilatory parameters worsen more than when compared to room air sedation. Niesters *et al*[3] demonstrated that while the deterioration in the ventilatory function was quite pronounced, the pulse oximetry continued to show normal readings.

In addition, it is insufficient to simply observe the patient's appearance and vitals to promptly and reliably detect the onset and extent of hypoventilation[4].

Fortunately, room air Pulse oximetry is quite sensitive in the detection of the onset of sedation-associated hypoventilation. It is a myth that capnometry offers any advantage over room air Pulse oximetry[5,6].

Supplemental oxygen prevents or delays oxygen desaturation resulting from hypoventilation induced by sedation. For similar reduction in pulse oximeter reading, hypercarbia is more pronounced in the setting of supplemental oxygen because of the longer duration of hypoventilation[7-9].

A supplemental oxygen-induced normal pulse oximetry reading creates a false sense of security for the person monitoring the patient and sets him or her up for a delay in the intervention directed towards improving ventilation in these early stages[10]. Desaturation is an effect: not to be "window dressed" without addressing the underlying process.

Due to hypoventilation, impaired clearance leads to increased partial pressure of CO_2 in the alveoli. Consequently, it becomes harder for the inspired oxygen to reach the alveoli, which may create a vicious cycle.

Inspired oxygen also reduces the hypoxic ventilatory drive, compounding the problem. Extreme elevation of CO_2 could produce CO_2 narcosis. Acute respiratory acidosis may develop with persistent hypoventilation.

It is a myth that short periods of hypoxemia, if detected and treated, improve clinical outcome. Review of available data of Pulse oximetry for perioperative monitoring has shown that researchers have repeatedly looked for such evidence and have not found it[11].

Hypoxemia is the effect of the hypoventilation, not the cause; therefore the measures solely directed towards delaying hypoxemia without addressing the hypoventilation will end up with higher likelihood of oversedation. In case of medications such as Midazolam and Fentanyl, the patient may continue to appear awake but progressive hypoventilation occurs. With propofol, early detection of hypoventilation is crucial in avoiding further dosing to stay within the therapeutic window.

The patients are appropriately advised to not use thick nail polish because it would reduce the sensitivity of the pulse oximetry sensor. It is remarkable that those who advocate avoidance of thick nail polish do not recognize the similarity between this recommendation and the fact that supplemental oxygen also markedly reduces the sensitivity and value of pulse oximetry in the setting of sedation.

The rationale given for using supplemental oxygen is that oxygen is essential for life; therefore, preventing any drop in oxygen saturation is a "safety" measure. However, a national study of cardiopulmonary unplanned events after GI endoscopy found that upon CORI (Clinical Outcomes Research Initiative) database review, routine use of supplemental oxygen was associated with significantly more Cardiopulmonary Unplanned

Events[12].

It is of concern that institutional policies and published studies have increasingly advocated and reported routine supplemental oxygen administration despite evidence that it is counterproductive has been available for more than a decade.

Pearl

Based on these facts and principles, the optimum approach may be to start sedation with the patient breathing room air (assuming no baseline hypoxemia on room air). The patient should be encouraged to take intermittent deep breaths to maintain ventilation. Airway management should be done as soon as the saturation drops by 4-6 points (from 100 to 96), as this is definitive evidence of hypoventilation and, therefore, the sedative effect. Avoidance or reduction of further sedative agent doses from this point onwards is prudent. If desaturation worsens, then ventilatory assistance along with supplemental oxygen is indicated. Oxygen alone, if ventilation is absent, does not correct the situation.

MYTH: SEDATION FOR GI PROCEDURES IN SLEEP APNEA PATIENTS IS VERY RISKY AND IS ASSOCIATED WITH A HIGHER INCIDENCE OF BAD OUTCOMES WITH STANDARD MONITORING

Indeed, patients with sleep apnea have added risk factors, but once known and incorporated in the management plan, current monitoring and care has produced equally good outcomes in this subset of the patients compared to non-sleep apnea patients[13-15].

Pearl

Patients with sleep apnea can safely receive procedural sedation, but they should be very closely watched as the risk of hypoventilation with sedation is higher and airway obstruction more likely. Room air pulse oximetry, small titrated doses, meticulous airway management and prompt use of reversal agents should be part of the plan.

MYTH: USE OF REVERSAL AGENTS DURING OR AFTER THE ENDOSCOPIC PROCEDURE IS A COMPLICATION, AND THE PATIENT MUST BE OBSERVED FOR LONGER PERIODS IN THE RECOVERY AREA DUE TO THE SIGNIFICANT RISK OF CLINICALLY DANGEROUS "REBOUND SEDATION"

Many institutions and regulatory agencies consider use of reversal agent such as Naloxone or Flumazenil to be "complications", requiring an incidence report that may even need to be reported to State regulatory agencies.

This myth implies that clinically inappropriate and avoidable oversedation must have occurred, because the reversal agent was required.

These policies and regulations also require extended intensive monitoring of these patients after use of a reversal agent, more than for other sedated patients who were not reversed. This policy is instituted to look for the mythical and dangerous "rebound sedation".

The following reasoning and data show that these are myths:

Sensitivity to the sedative agents is known to have a wide range of variability. A relatively small dose may lead to unexpected profound respiratory depression. In this setting, reversal of this effect is a safety measure, not a complication, *e.g.,* tapping on the brakes while driving through traffic is hardly proof of speeding.

There are times during many procedures, particularly colonoscopies, where increasing doses of Fentanyl or Midazolam are needed to counter the discomfort related to the pressure of the scope through a tortuous segment of the colon. However, once the discomfort has abated due to straightening of the colonic segment or at the end of the procedure, the unopposed residual sedative effects of these medications manifest due to the duration of the action of the drug. A reversal agent would promptly mitigate the effects of the drug. Moreover, ongoing analgesia after completion of the procedure is not needed, in contrast to after traditional surgery.

It is also a myth that these patients need to be routinely observed for extended periods (much longer than usual) after use of the reversal agent.

Bad outcomes due to Rebound sedation after reversal agent use, even after a massive overdose in the setting of poisoning, accidental or otherwise, are extremely rare[16,17].

Because titrated doses of short-acting sedatives are used in the GI lab, clinical practice experiences and reported studies in the medical literature have shown this practice to be very safe. Studies reporting routine use of reversal agents showed no clinically significant rebound sedation[18,19].

Resedation was reported in one study[20], but those patients remained clinically stable; return to the hospital and additional medical interventions were not required.

Pearl

The use of reversal agent is a safety measure. Despite the reversal agent having a shorter duration of action than the drug reversed, dangerous rebound sedation is not encountered in clinical setting due to continued metabolization and clearance of the sedative agent during this time.

Individualizing the observation based on clinically-unusual recovery is advisable over an indiscriminately prolonged observation policy after use of reversal agents.

MYTHS RELATED TO HOW MUCH MONITORING EQUIPMENT IS REQUIRED TO SAFELY PERFORM THE ENDOSCOPIC PROCEDURAL SEDATION

Current monitoring practices include Pulse oximetry, intermittent blood pressure recording, continuous electrocardiogram tracing, and, in some instances, Capnography and Bispectral Index.

In the United States Endoscopy labs, continuous cardiac monitoring is virtually universal. Around the world, this is not very common. The discrepancy has not been associated with any worsening of the outcome.

It is recommended that one nurse be dedicated exclusively to monitor the patient during sedation.

No studies have ever shown an outcome advantage from any of these recommendations of monitoring practices.

How much monitoring is sufficient to avoid sedation related serious complications? Külling *et al*[21] provided data in the setting of Propofol-based sedation in the GI lab without presence of anesthesia personnel.

This large study showed that by monitoring the patients with a Pulse oximeter alone, (no cardiac or blood pressure monitoring), along with a single nurse monitoring the patient as well as assisting the endoscopist, more than 27000 procedures were performed under gastroenterologist-directed Propofol, without significant complications.

Room air pulse oximetry has been demonstrated to be clinically as effective as Capnometry[6] and Bispectral Index[22] in monitoring for hypoventilation in these patients.

Pearl

Monitoring should be optimized. Room air Pulse oximetry along with good airway management may be sufficient for the vast majority of patients. Artifacts and malfunctions of monitoring devices (electrocardiogram, *etc.*) should not be allowed to become a distraction during the monitoring of endoscopic procedures.

MYTH: IMPLANTED DEFIBRILLATORS AND PACEMAKERS NEED TO BE RESET IF ELECTRO-CAUTERY IS USED DURING THE ENDOSCOPIC PROCEDURES

Implanted Defibrillators are commonly turned off and presumed to be at risk for accidental activation by electrocautery in many GI labs. This is an example of not incorporating the advances in technology and accumulated evidence into the current guidelines. Guidelines have remained in place for a long time after the technological changes have made them obsolete and erroneous. Devices currently in use are shielded and do not sense the electrocautery as a dysrhythmia[23,24].

Pearl

Newer Defibrillators and pacemakers do not require any adjustment for GI procedures. It is a good practice to avoid placing cautery pads close to the defibrillator device.

Despite initial concerns, Capsule endoscopy also has not been found to interfere with these devices, nor does pacemaker affects imaging done with Capsule endoscopy[25,26].

Capsule endoscopy may be safely undertaken in patients with pacemakers and implanted defibrillators.

MYTH: PROPOFOL USE UNDER THE DIRECTION OF GASTROENTEROLGISTS IS UNSAFE; ITS USE BY ANESTHESIA SPECIALISTS IS SAFER

This myth is quite prevalent in the United States and some other parts of the world, whereas in many other places, including Switzerland, increasing adoption of Propofol by the gastroenterologist has been reported[27]. On this issue, extensive data is available, spanning more than a decade. A team of a gastroenterologist and registered nurses has provided Propofol-based sedation with remarkable safety, excellent patient experience and without the additional cost of anesthesia personnel[28,29].

On the other hand, Gangi *et al*[30], in his study, found that Propofol given by anesthesia personnel was associated with a higher complication rate. This may be due to their practice of using larger doses (for induction of the General anesthesia that is followed by assisted ventilation), whereas the endoscopy patients are expected to breathe on their own[31].

The argument is commonly made that Propofol package insert restricts its administration solely to formally trained anesthesia personnel.

However, the actual phrase published by the manufacturer states:

"For general anesthesia or monitored anesthesia care (MAC) sedation, (emphasis added) DIPRIVAN Injectable Emulsion (Propofol) should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure." DIPRIVAN® (Propofol) INJECTABLE EMULSION, USP Fresenius Kabi USA, LLC Revised 5/14.

The gastroenterologists do not use Propofol for General anesthesia or MAC, and, therefore, the requirement of these abilities is not applicable in this setting[32-34].

For example, many primary physicians have acquired the skill to perform flexible sigmoidoscopy. Their use of a (longer) colonoscope in the GI lab would not be questioned or prohibited as long as the colonoscope is used to perform only flexible sigmoidoscopy.

Pearl

Propofol has been used by Gastroenterologists around the world for more than a decade with remarkable safety and patient satisfaction. It should be an option for interested and skilled physician and nurse teams. It should be undertaken after adequate training of the entire team. Patient safety should be the highest priority. This can be accomplished by learning the pharmacology of the drug and using small titrated doses (with or without combination with small doses of other agents that can be reversed) along with room air pulse oximetry to promptly detect hypoventilation.

MYTH: PROPOFOL LEADS TO DEEP SEDATION, WHEREAS NARCOTICS AND BENZODIAZEPINES PROVIDE MODERATE SEDATION

As reported by Patel *et al*[35], deep sedation frequently occurs in the GI lab with Narcotics and Benzodiazepines during sedation given by gastroenterologists and is routinely managed by them. On the other hand, Cohen *et al*[33] and Sipe *et al*[34] have reported that a moderate level of sedation is consistently achievable with low-dose Propofol-based sedation.

Many sedative agents, if given in large enough doses, lead to a state of general anesthesia. A general anesthetic, alcohol, has been available worldwide (over the counter) for centuries!

Pearl

Depth of sedation is age and dose dependent and exhibits a wide variability. The therapeutic effect and side effects are potentiated when these agents are combined. It is not the agent, but how and to what effect it is used that should be the focus.

MYTH: ENDOTRACHEAL INTUBATION SKILL IS NECESSARY FOR GI SEDATION WITH PROPOFOL

It is a myth because due to ultra short duration of action of the drug, and in the setting of smaller titrated doses, the transient respiratory depression from Propofol is likely to dissipate well before the intubation equipment can be assembled and used. If apnea does occur, then ambu bag ventilation is effective in assisting ventilation for a short duration.

Pearl

An ambu bag and oxygen should always be immediately available, and the team must practice regularly to stay skilled for its effective use. Early recognition of hypoventilation and proper airway management should further reduce the incidence of rare events when assisted ventilation is required.

MYTH: FOR PATIENTS WITH PROSTHETIC JOINTS, ENDOSCOPY FREQUENTLY LEADS TO INFECTION AND PROPHYLACTIC ANTIBIOTICS ARE ESSENTIAL

The Orthopedic Surgical Society has recommended giving antibiotics prior to endoscopic procedures[36].

However, current Endoscopy society guidelines[37], after reviewing the available clinical data, recommends against it.

Despite the fact that endoscopies without prophylactic antibiotics have been routinely performed worldwide for last several decades, without adhering to the Orthopedic Surgical Society recommendations, only a couple of joint infections have been reported in this setting, that could be coincidental.

The real and frequent risks and other implications of unnecessary antibiotic use must be weighed against this rare event. Antibiotics should not be given solely for an unproven theoretical protective effect[38].

Pearl

This issue should be discussed with each patient and the risk of infection should be put in proper perspective. This should help in avoiding prophylactic antibiotics of questionable benefit in this setting.

CONCLUSION

Neither "expert recommended" nor "increasingly adopted" practices and policies are immune from being fallacies and myths. In the Endoscopy suite, arguably the most significant inappropriate practice is the routine use of Supplemental oxygen because it is a practice contrary to the physiologic and scientific data with demonstrated adverse effects. It puts ventilatory monitoring by Pulse oximetry at a disadvantage. All of us should review in depth research on these issues and develop a mindset of continually questioning and re-examining the policies and practices in light of scientific data as well as technological advancements, *e.g.*, shielded implanted defibrillators related to electrocautery.

"The chief cause of poverty in science is imaginary wealth. The chief aim of science is not to open a door to infinite wisdom, but to set a limit to infinite error." Bertolt Brecht: Life of Gallileo.

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P- Reviewer: Kurtoglu E, Slomiany BL **S- Editor**: Tian YL
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DOI: 10.4253/wjge.v6.i12.592

World J Gastrointest Endosc 2014 December 16; 6(12): 592-599
ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic resection of subepithelial tumors

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Received: August 15, 2014 Revised: October 3, 2014
Accepted: October 28, 2014
Published online: December 16, 2014

Abstract

Management of subepithelial tumors (SETs) remains challenging. Endoscopic ultrasound (EUS) has improved differential diagnosis of these tumors but a definitive diagnosis on EUS findings alone can be achieved in the minority of cases. Complete endoscopic resection may provide a reasonable approach for tissue acquisition and may also be therapeutic in case of malignant lesions. Small SET restricted to the submucosa can be removed with established basic resection techniques. However, resection of SET arising from deeper layers of the gastrointestinal wall requires advanced endoscopic methods and harbours the risk of perforation. Innovative techniques such as submucosal tunneling and full thickness resection have expanded the frontiers of endoscopic therapy in the past years. This review will give an overview about endoscopic resection techniques of SET with a focus on novel methods.

Key words: Subepithelial tumors; Submucosal tumors; Gastrointestinal stromal tumors; Endoscopic resection; Endoscopic full thickness resection

Core tip: This review gives an overview about current endoscopic management of subepithelial tumors. Endoscopic resection techniques, available clinical data and potential indications will be discussed in detail. The review focuses on novel advanced techniques like submucosal tunnelling and endoscopic full thickness resection.

Schmidt A, Bauder M, Riecken B, Caca K. Endoscopic resection of subepithelial tumors. *World J Gastrointest Endosc* 2014; 6(12): 592-599 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/592.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.592

INTRODUCTION

Subepithelial tumors (SETs) are mainly asymptomatic and incidentally found during endoscopic examinations in about 0.3% of cases[1]. The term "submucosal tumors" is widely used but incorrect as many tumors arise from or infiltrate deeper layers of the gastrointestinal (GI) wall. SET include a variety of benign, premalignant or malignant lesions. Although the majority of those lesions is benign, 13% are malignant[2].

Endoscopic ultrasound (EUS) has improved differential diagnosis of these tumors but a definitive diagnosis on EUS findings alone can be achieved in the minority of cases[3]. Hypoechoic tumors originating from the muscularis mucosae or the muscularis propria are consistent with leiomyomas or gastrointestinal stromal tumors (GIST). Although certain EUS criteria have been described to differentiate Leiomyomas and GIST[4], tissue sampling is generally needed to obtain definitive histologic diagnosis. For small tumors, diagnostic yield of EUS-guided biopsy is low[3]. Moreover, even if GIST is diagnosed, the amount of tissue gained is usually not sufficient to definitively determine mitotic count for appropriate risk stratification[5,6]. Therefore, complete endoscopic resection may provide a reasonable approach for tissue acquisition.

According to current NCCN guidelines, GIST $\geqslant$ 2 cm should be resected surgically whereas GIST < 2

cm lacking high-risk features in EUS can be followed-up periodically[7]. However, discrimination between "benign" and malignant GIST based on EUS-features may be difficult. Moreover, follow-up intervals are not well defined and many patients may not wish to undergo repeated life-long endoscopies. Therefore, European and Japanese guidelines recommend resection of histologically proven GIST even if size is < 2 cm[8,9]. Surgical resection is the gold standard for these tumors. However, endoscopic resection provides both a definitive histologic diagnosis (including risk stratification) and may also be an effective minimally invasive treatment for these potentially malignant lesions. Innovative advanced resection techniques such as submucosal tunneling and full thickness resection have expanded the frontiers of endoscopic therapy in the past years[10]. This review will describe endoscopic resection techniques of SET with a focus on novel methods.

ROLE OF EUS FOR CHOICE OF RESECTION MODALITY

As described above, EUS is a valuable tool for differential diagnosis of SET. In addition, thorough EUS-evaluation is mandatory to select the appropriate resection strategy depending on (1) tumor size: Tumor size can be determined exactly by EUS. With increasing size, endoscopic resection usually gets more demanding and may require advanced resection techniques. Moreover, peroral en bloc extraction of tumors > 3 cm may be difficult; (2) layer of origin: Exact determination of the originating layer or extent of tumor infiltration into the GI wall is mandatory for selection of resection modality. Basic resection techniques like cap-assisted resection suffice for tumors restricted to the submucosa. Resection of tumors originating from or infiltrating the MP is more challenging due to the risk of GI wall perforation. In these cases, EUS can also give information about the extent of tumor connection (broad or narrow) and depth of infiltration of the MP[11]; and (3) growth pattern: EUS can determine growth pattern with respect to the GI wall. Whereas tumors with intraluminal growth are usually suitable for endoscopic resection, tumors with predominantly extaluminal growth may require surgical therapy.

ENDOSCOPIC RESECTION TECHNIQUES

Snare resection

Small (1-2 cm) pedunculated or sessile SETs can be resected with a snare with or without prior injection[1]. One of the first series published reported on 45 patients with small submucosal lesions, all of which were resected successfully without any complications using a one or two channel endoscope (with a forceps to lift the lesion)[12]. A second series with 54 cases reported on diagnostic snare resection of submucosal tumors with a success rate of 100%, bleeding occurred in 9% of patients, no perforations were reported[13].

Cap-assisted submucosal resection

Cap-assisted submucosal resection is a simple and time-effective technique for small tumors limited to the submucosa. The tumor is sucked into a transparent cap and then resected with a mucosectomy snare preloaded in the cap. Alternatively, band ligation can be used to create a pseudopolyp prior to snare resection. Maximum size of the tumor is limited by the inner diameter of the cap which generally does not exceed 11 mm. In a study by Kajiyama *et al*[14] endoscopic submucosal resection without band ligation was reported to be feasible and effective for small esophageal leiomyomas originating from the muscularis mucosae. Feasibility of submucosal resection after band ligation was demonstrated by Wehrmann *et al*[15] in a prospective study for submucosal esophageal tumors. Maximum tumor size was 13 mm and R0-Resection was achieved in 10/11 cases. Lee *et al*[16] reported successful resection of esophageal lesions with a mean size of 7.1 mm (range 3-12 mm) with R0 resection in 96% and a mean procedure time of 5 min 26 s.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is an established technique for resection of gastric or colorectal neoplasms. After circumferential mucosal incision, step-by-step dissection of submucosal and muscular fibres with different electrosurgical knifes allows precise en-bloc resection of tumors. The technique has been used for resection of SET originating from the MP. In this context, it has also been called "endoscopic muscularis dissection", "endoscopic enucleation" or "endoscopic submucosal excavation"[10,17,18]. The largest study in this field was recently published by a He and colleagues. 145 patients with gastric SET arising from the MP with an average diameter of 15.14 mm (range 3-50) underwent ESD. Complete resection rate was 92%. Perforation occurred in 14%, all of which could be managed endoscopically[19]. A Chinese study included 143 patients with SET of the esophagogastric junction arising from the MP. Histologically complete en bloc resection could be achieved in 94.4%, perforation rate was 4.2%[20]. Other studies report success rates of 68%-100% with perforation rates of 2.4%-13.3%[21-26]. In conclusion, ESD appears to be an effective technique for resection of SET up to a size of 50 mm. However, the technique is technically demanding and may be time consuming. Moreover, for tumors arising from the MP, perforation rates up to 15% even in experienced hands have been reported. Lesions fixed to to the MP exhibit an increased risk of perforation when compared to lesions with a positive rolling sign[22]. Although extent of connection to the MP has not shown to be associated with increased risk of perforation[22], thorough EUS evaluation is mandatory prior treatment.

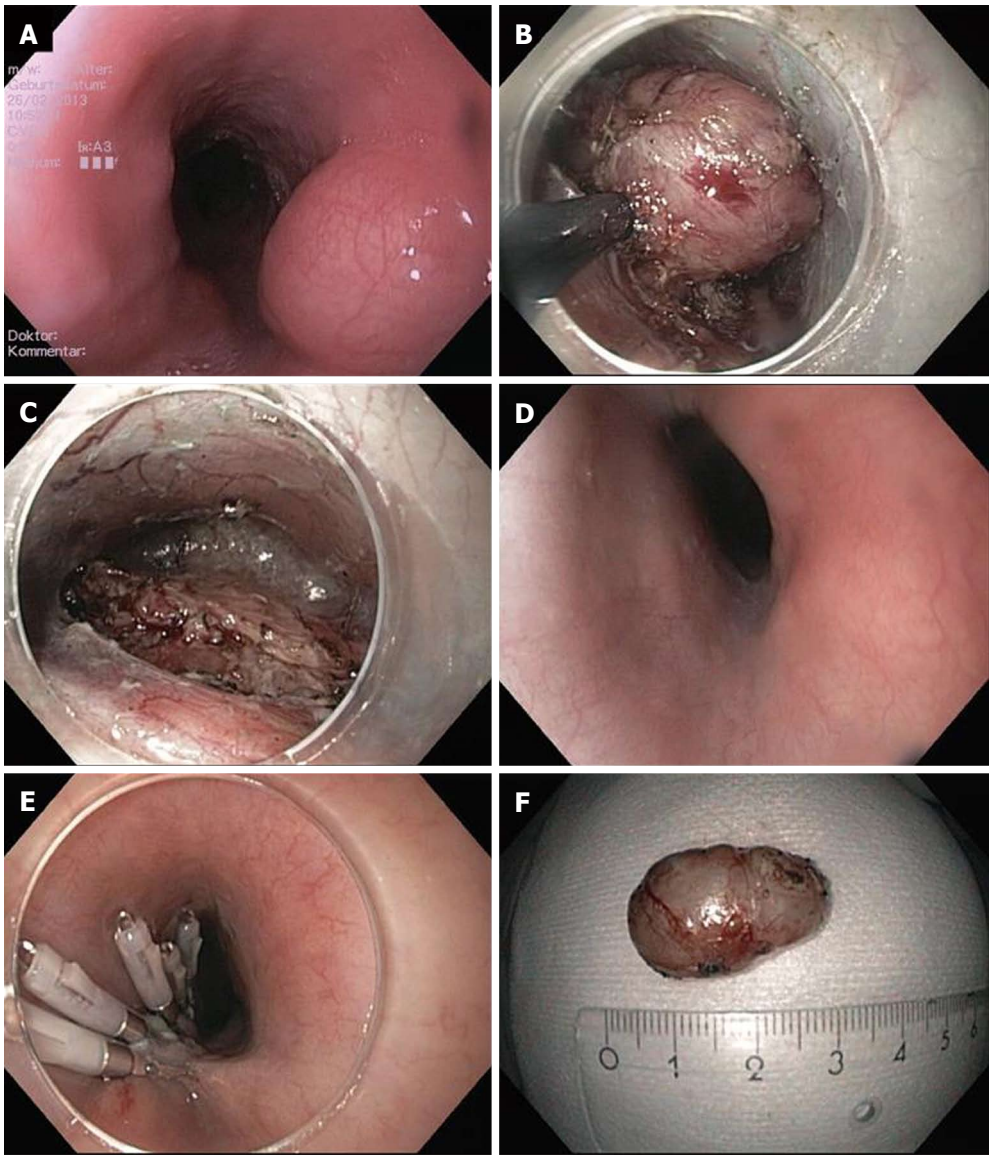

Figure 1 Submucosal endoscopic tumor resection/tunneling technique. A: Endoscopic image of lumen obstruction subepithelial tumor in the proximal esophagus in a 42 years old woman with dysphagia; B: After preparing the submucosal tunnel, the tumor gets visible and is enucleated in endoscopic submucosal dissection-technique with a TT knife. The tumor was arising from the muscularis propria; C: Resection site (endoscope in the submucosal tunnel). The muscularis propria is excised/perforated; D: Resection site (endoscope in the esophageal lumen. Intact mucosa completely covers the muscular perforation; E: The mucosal incision (about 5 cm proximal tot he resection site) was closed with standard clips; F: Resection specimen. Histological examination revealed a Leiomyoma, which had been R0-resected.

Submucosal endoscopic tumor resection/submucosal tunneling

The concept of "submucosal tunnelling" in the esophagus was initially described for peroral endoscopic myotomy (POEM) procedure by Inoue *et al*[27] in 2010. Only a few years later, this technique was applied for resection of subepithelial tumors in the esophagus and in the cardia[28,29]. In analogy to the POEM procedure, a mucosal incision at least 5 cm proximal to the tumor is created and the endoscope is introduced into the submucosal space. Then, the submucosal fibres are dissected until the tumor gets visible in the tunnel. The tumor is subsequently enucleated in ESD technique. During tunnelling and enucleation, it is crucial not to perforate the mucosa. After extracting the tumor from the tunnel, the mucosal incision is finally closed with standard clips (Figure 1).

Submucosal endoscopic tumor resection is especially suitable for tumors originating from or infiltrating into the MP. Compared to conventional ESD, a major advantage of this novel technique is that a mucosal layer covers the resection site and protects from mediastinitis/peritonitis when intended or accidental perforation of the MP occurs.

The largest study published to date included 85 SET (60 esophageal and 9 gastric). The tumors were mainly arising form the superficial MP (88.2%) and had a mean size of 19.2 mm (range 10-30 mm). Complete resection was achieved in 100% of cases with a mean procedure time of 57.2 min. Pneumothorax occurred

Figure 2 FTRD (Full Thickness Resection Device, Ovesco Endoscopy, Tübingen Germany). The device is assembled on a standard colonoscope. It consists of 14 mm modified over-the-scope clips which is mounted on a long transparent cap. A monofilament snare is preloaded in the tip of the cap. The handle of the snare runs on the outer surface of the endoscope underneath a transparent sheath. A grasping forceps or a tissue anchor can be advanced through the working channel of the endoscope.

in 7.1%, subcutaneous emphysema in 9.4% and pneumoperitoneum im 4.7%[30]. Other smaller studies reported success rates between 78% and 100% and complication rates between 13% and 33%[18,29,31,32]. The most common complications reported are pneumothorax, subcutaneous and mediastinal emphysema and pneumoperitoneum. While occurrence of pneumothorax generally requires a chest drain, air leakage into the mediastinum, the abdominal cavity and the subcutaneous tissue may not be considered as a "complication" rather than a natural consequence when the MP is perforated/resected. As long as the covering mucosa over the perforation is preserved, leakage of esophageal or gastric content is prevented. In the clinical studies published to date, no severe intraabdominal or mediastinal infections have been reported. Hence, submucosal endoscopic tumor resection using a tunnelling technique is feasible and relatively safe for tumors originating from the MP in the esophagus and cardia. Although a few gastric cases are also reported, submucosal tunnelling requires a relatively straight endoscope position and may not be applicable for tumors in locations like the fundus or proximal corpus.

Endoscopic full thickness resection

For SET arising from or infiltrating deep layers of the MP, full thickness resection may be necessary to achieve complete removal of the tumor. As full thickness resection naturally results in a GI wall perforation, secure and effective defect closure is mandatory. Generally, there are two different approaches for endoscopic full thickness resection (EFTR): (1) Full thickness resection followed by endoscopic defect closure; and (2) Creation of GI wall duplication (with serosa-to-serosa apposition) followed by EFTR.

Zhou *et al*[33] reported full thickness resection of 26 gastric SETs arising from the MP. Resection/enucleation of the tumors was performed using ESD technique and the gastric wall defect was closed with standard clips. Mean tumor size was 2.8 cm (1.2-4.5 cm). Complete resection rate was 100% with a mean procedure time of 105 min; no major complications were reported. Another study from 2013 reported 20 on a similar resection technique in 20 patients. In this study, the wall defects were closed with clips and endoloops[34]. *En bloc* resection rate was 100% without severe complications. A Chinese study reported on 42 gastric stromal tumors which were resected either by EFTR with secondary clip closure or laparascopically. In this non-randomized study, complete resection rate, operation time, length of hospital stay and complications were not statistically different in both groups[35].

Although the studies mentioned report excellent results with no serious complications, it must be emphasized that defect closure with standard clips may only be possible for small perforations. Moreover, concerns have been raised whether closure of only the mucosal layer is sufficient after EFTR[36]. Von Renteln and colleagues compared closure of natural orifice transluminal endoscopic surgery (NOTES) gastrostomies by either conventional or over-the-scope clips (OTSC) in a porcine study with 20 pigs[37]. In the conventional clip group, 3 minor and 1 major leaks were observed and four pigs developed peritonitis. In the OTSC group, no leaks were observed and microscopic evaluation showed that OTSC led to a deeper defect closure within the submucosal or muscular layer. Multiple clinical studies have shown effectivity of OTSC for durable closure of GI wall perforations[38]. EFTR with consecutive defect closure with OTSC was clinically evaluated in the EndoResect study[39]. Twenty patients with gastric SET $\leqslant$ 3 cm were enrolled; six tumors could not be resected endoscopically due to large size or extraluminal growth. The other tumors were resected using a double channel endoscope, a tissue retractor and a monofilament snare. Perforation occurred in six cases, all of which could be closed by OTSC application; mean procedure time was 44 min. Although this approach is very interesting because of its technical simplicity, most of the procedures in the study were done under laparoscopic control. Moreover, OTSC application requires secure apposition of the borders of the gastric defect which may not be possible in case of large perforations.

Even if clinical data suggest that EFTR with secondary defect closure is feasible and safe, secure closure of the GI wall may be technically demanding and strongly depends on the skills and the experience of the endoscopist[10]. Therefore, securing GI wall patency before resection (in analogy to laparoscopic wedge resection) may be an interesting and potentially safer approach. The concept of OTSC application over a SET followed by snare resection above the clip was recently reported by a United States group[40,41]. Lesions were located in the duodenum, in the esophagus, in the stomach and in the rectum. After application of an 11 mm OTSC, all lesions could be resected successfully. R0-resection was achieved in 7/8 cases. A drawback of this

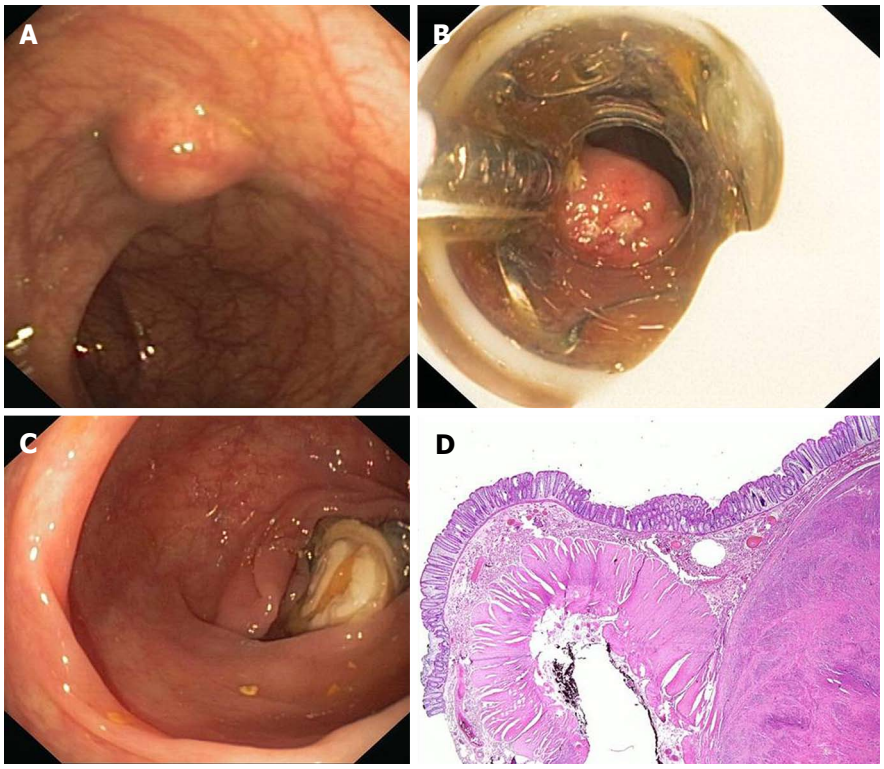

Figure 3 Endoscopic full thickness resection with the FTRD. A: A 75 years old woman presented with a 1.5 cm subepithelial tumor in the descending colon; B: Endoscopic view with the FTRD mounted on a standard colonoscope; C: Resection site after endoscopic full thickness resection. The over-the-scope clips secures colonic wall patency; D: Histologic image (HE-staining) of the resection specimen showing one lateral resection margin. Note the cross-sectional view of the whole colonic wall on the left side. The tumor (leiomyoma) is shown on the right.

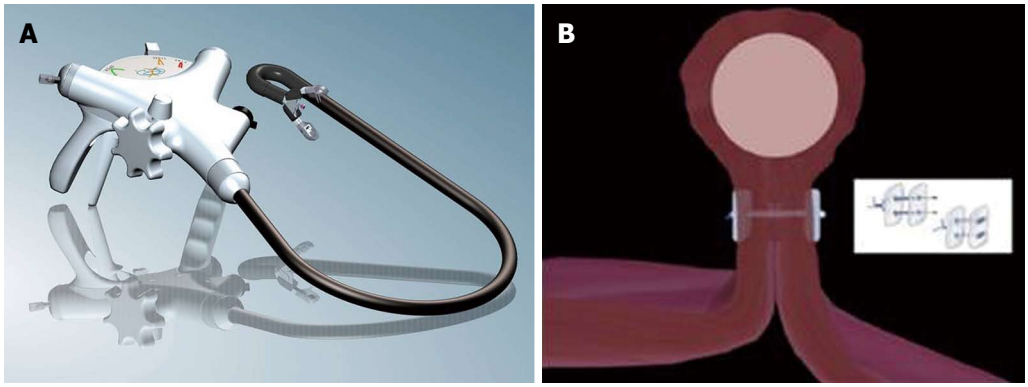

Figure 4 Endoscopic full thickness suturing. A: The GERDX suturing device (G-Surg, Seeon, Germany); B: Schematic illustration of full thickness suturing. Application of PTFE-pledgeted sutures underneath the tumor creates a gastric wall duplication with serosa-to-serosa apposition.

technique is that the size of the cap limits the maximum size of the lesion (mean size in the study was 13.4 mm). A novel over-the-scope device (FTRD, Ovesco Endoscopy) uses a modified 14 mm OTSC mounted on a long transparent cap with a preloaded snare (Figures 2 and 3)[42-45]. This device has been designed for one-step full thickness resection using a clip-and-cut technique. Due to the larger diameter of the OTSC and the longer cap, resection of larger lesions is possible compared to the standard OTSC system. The device was investigated by von Renteln *et al*[44] for resection of artificial submucosal lesions in a porcine study. The OTSC was able to close the resection site completely in all cases, however, EFTR was achieved in 50% of cases only. This is probably due to the fact that the thick gastric wall can often not fully be incorporated into the cap with its inner diameter of 13 mm. Another drawback of the device is its large outer diameter of 21 mm which hampers peroral introducability. Two porcine studies evaluated the device for use in the colon and showed that EFTR was feasible with efficient OTSC closure of the defects. Maximum size of resection specimen was 30 and 40 mm. In our first clinical experience (25 patients, manuscript submitted), colorectal EFTR with the FTRD was effective and safe. Due to the limitations in the upper GI tract, the FTRD is currently CE marked exclusively for colorectal EFTR.

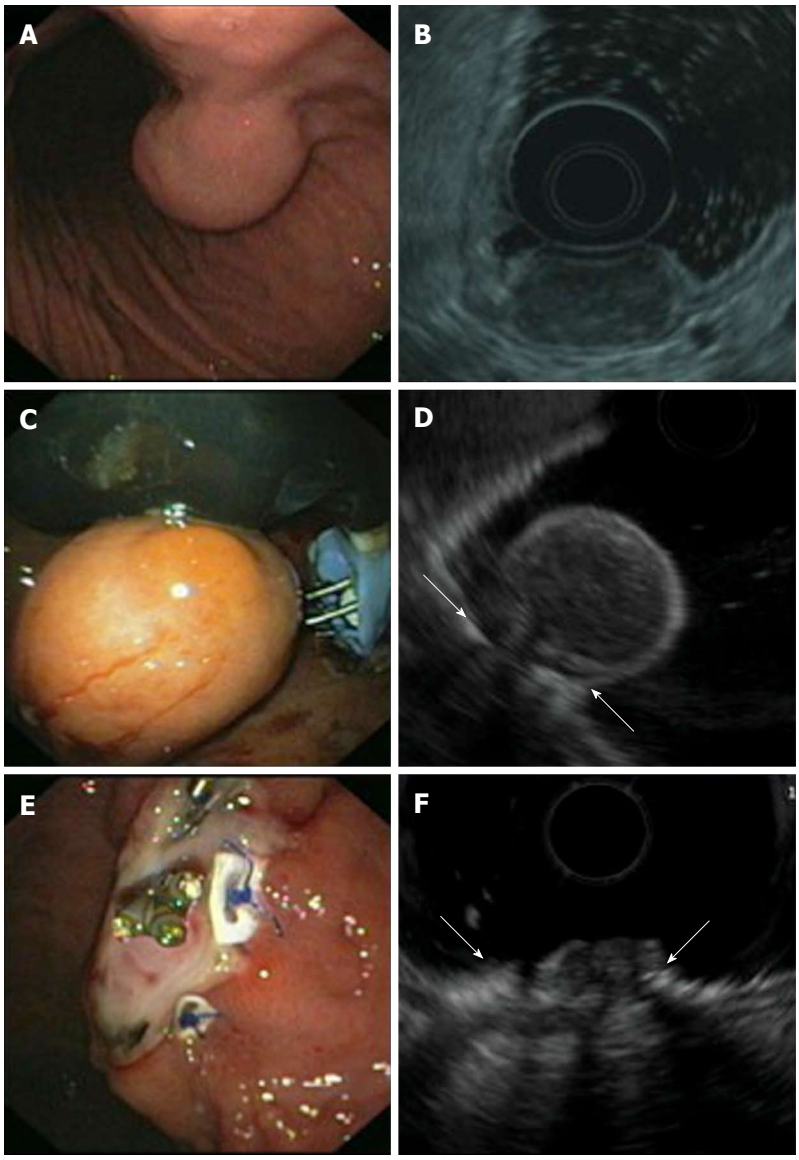

Figure 5 Endoscopic full thickness resection of gastric gastrointestinal stromal tumors after transmural suturing. A: Subepithelial tumor in the gastric corpus; B: Endoscopic ultrasound (EUS) showed a hypoechoic tumor originating from the muscularis propria with a maximum diameter of 27 mm; C: Two transmural sutures underneath the tumor were applied using the Plicator™ suturing device; D: EUS image of the pseudopolyp after suturing. Arrows are indicating the sutures; E: The tumor was resected with a snare above the sutures. The transmural PTFE-pledgeted sutures are securing gastric wall patency. Resection was macroscopically complete; F: EUS image of the resection site. Arrows are indicating the sutures. There was no evidence of residual tumor.

In 2008, our group reported on the concept of applying transmural sutures underneath the tumor prior EFTR for the first time. Two transmural PTFE-pledgeted sutures were placed underneath the tumor using a device originally designed for endoscopic anti-reflux Therapy (Plicator™, NDO Surgical, Inc, Mansfield, Mass) thereby creating a full thickness duplication with serosa-to-serosa apposition (Figure 4). The tumor was then resected with a monofilament snare above the suture (Figure 5)[46]. In 2011, a second series with three patients undergoing successful EFTR with the use of resorbable sutures was published[47]. In the meantime, our group has applied this technique for EFTR of subepithelial gastric tumors in a total of 31 patients [Schmidt *et al*, manuscript accepted in Endoscopy]. Mean tumor size was 20.5 mm (range 8-48). Macroscopically complete en bloc resection could be achieved in 100%, R0-resection rate was 90.3% with a median procedure time of 60 min. Perforation occurred in three patients; in all cases, the defect was successfully closed by application of additional transmural sutures. When compared to OTSC application before resection, this method is applicable for tumors up to a size of about 4 cm. Moreover, it is feasible in almost every location in the stomach. As the suturing device was originally designed to work in retroflex position, the technique is especially suitable for tumors in the proximal corpus, cardia and even in the fundus. In comparison to the clip closure techniques described above, patency of the gastric wall is secured not only by mucosal closure but rather by full-thickness suturing with serosa-to-serosa apposition. This technique meets surgical standards for defect closure and may result in a more durable gastric

wall repair especially for resection of large tumors. The suturing device can not only be used for suturing prior resection but also for secondary perforation closure[48]. A major limitation of EFTR after transmural suturing is the need of special endoscopic equipment. The Plicator™ device from NDO is not any more commercially available. However, a new CE-marked single-use device is available in Europe now (GERDX™, G-Surg, Seeon, Germany). This device was used for the last two cases in our series and seems to be as effective as the Plicator™.

CONCLUSION

Surgical resection is still standard of care for resection of malignant SET. However, novel advanced resection and closure techniques have led to shift from mucosal and submucosal resections towards intramural and transmural endoscopic interventions. Although clinical data is still very limited, the results published so far are promising. However, prospective comparative studies are necessary to further evaluate efficacy, safety, and long-term outcome of these techniques.

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P- Reviewer: Camellini L, Zhou XD **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Zhang DN

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DOI: 10.4253/wjge.v6.i12.600

World J Gastrointest Endosc 2014 December 16; 6(12): 600-605
ISSN 1948-5190 (online)

RETROSPECTIVE STUDY

Narrow-band imaging observation of colorectal lesions using NICE classification to avoid discarding significant lesions

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Supported by Institute of Minimally Invasive Endoscopic Care (iMEC), Sano Hospital, No. 2014-02
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Received: June 28, 2014 Revised: October 31, 2014
Accepted: November 7, 2014
Published online: December 16, 2014

Abstract

AIM: To assess the risk of failing to detect diminutive and small colorectal cancers with the "resect and discard" policy.

METHODS: Patients who received colonoscopy and polypectomy were recruited in the retrospective study. Probable histology of the polyps was predicted by six colonoscopists by the use of NICE classification. The incidence of diminutive and small colorectal cancers and their endoscopic features were assessed.

RESULTS: In total, we found 681 cases of diminutive (1-5 mm) lesions in 402 patients and 197 cases of small (6-9 mm) lesions in 151 patients. Based on pathology of the diminutive and small polyps, 105 and 18 were non-neoplastic polyps, 557 and 154 were low-grade adenomas, 18 and 24 were high-grade adenomas or intramucosal/submucosal (SM) scanty invasive carcinomas, 1 and 1 were SM-d carcinoma, respectively. The endoscopic features of invasive cancer were classified as NICE type 3 endoscopically.

CONCLUSION: The risk of failing to detect diminutive and small colorectal invasive cancer with the "resect and discard" strategy might be avoided through the use of narrow-band imaging observation with the NICE classification scheme and magnifying endoscopy.

Key words: Image-enhanced endoscopy; Narrow-band imaging; Resect and discard; NICE classification; Magnifying endoscope; Colonoscopy; SM-d

Core tip: Discarding a polyp without performing histological evaluation runs the risk of failing to detect small invasive colorectal cancer. Retrospectively, we aimed to assess the risk of failing to detect diminutive and small colorectal invasive cancer with the "resect and discard" strategy by using the NICE classification scheme with a magnifying endoscope. We reviewed and assessed 878 polyps less than 1 cm in diameter detected in our hospital. Among them, 2 SM-d carcinomas were found and both of their optical features were classified as NICE type 3. We concluded

that the risk of failing to detect diminutive and small invasive colorectal cancer with the "resect and discard" strategy might be prevented by employing NICE classification under narrow-band imaging magnification.

Hattori S, Iwatate M, Sano W, Hasuike N, Kosaka H, Ikumoto T, Kotaka M, Ichiyanagi A, Ebisutani C, Hisano Y, Fujimori T, Sano Y. Narrow-band imaging observation of colorectal lesions using NICE classification to avoid discarding significant lesions. *World J Gastrointest Endosc* 2014; 6(12): 600-605 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/600.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.600

INTRODUCTION

Removal of all adenomatous polyps during colonoscopy has been standardized worldwide. As the National Polyp Study (NPS) demonstrated that removal of all adenomatous polyps could significantly reduce colorectal cancer incidence and mortality[1], it has been standard practice for all polyps to be retrieved and submitted for pathological evaluation. Recently, however, the "resect and discard" policy was advocated[2,3]. According to this strategy, a hyperplastic polyp in recto-sigmoid colon would be left to reduce the risk of polypectomy, and diminutive (1-5 mm) or small (6-9 mm) lesions would be resected and discarded to eliminate the costs associated with histological evaluation. However, discarding polyps without performing histology runs the risk of failing to detect diminutive and small colorectal invasive cancer, which would otherwise be received surgery. Recently, the NICE classification was proposed as a valid tool for not only differentiating hyperplastic from adenomatous polyps, but also predicting SM-d carcinomas in colorectal tumors[4,5].

The aim of this study was to investigate the risk of failing to detect diminutive and small colorectal invasive cancers in real-time using the "resect and discard" strategy with NICE classification and magnifying endoscopy.

MATERIALS AND METHODS

Patients

Consecutive patients who underwent colonoscopy and received polypectomy in our institution were recruited in the retrospective study.

Colonoscopy procedure

For bowel preparation, patients ingested 1.5 to 2 L of polyethylene glycol solution in the morning before the procedure. Six colonoscopists performed all colonoscopy procedures up to the cecum with high-resolution endoscope (CF-H260AZI; Olympus, Optical Co., Ltd., Tokyo, Japan) and NBI magnification. We used a video endoscope system (EVIS LUCERA SPECTRUM; Olympus, Optical Co., Ltd., Tokyo, Japan) and a digital image filing system (SolemioENDO; OLYMPUS, Tokyo, Japan). In NBI mode with this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm. We set the optical enhancement at enhancement mode A8 and color mode 3. Macroscopic type of the lesions were based on the Paris classification of superficial gastrointestinal lesions[6].

Endoscopic diagnosis using the NICE classification

All of the lesions were initially detected by conventional view, and then examined by NBI with magnification to evaluate the endoscopic features on the surface. All lesions were then classified into 3 types based on NICE classification, which consists of 3 types as shown in Table 1 and Figure 1[4,7].

Clinicopathological evaluation

We reviewed medical records using SolemioENDO colonoscopy system and detected polyps less than 1 cm in diameter, and we aggregated the lesion size data (1-5/6-9 mm), location (right/left-side), shape (pedunculated/sessile/flat/depressed), NICE classification category, and pathological diagnosis. The incidence of diminutive and small invasive colorectal carcinoma and their endoscopic features were also assessed.

RESULTS

Patient characteristics and clinicopathological features of resected lesions

A total of 878 polyps less than 1 cm in diameter were detected in 468 patients. Among the cohort, 290 patients were male, 178 were female, and average age was 66.3 years old (32-97, SD). The average value of polyp size was 4.7 mm (1-9, SD) and 542 of them were detected in the right-side colon, while 336 were detected in the left side. A total of 12 polyps were pedunculated, 274 were sessile, 590 were flat, and 2 were depressed in shape. Based on histology, 123 were non-neoplastic polyps [100 hyperplastic, 13 Sessile Serrated Adenoma/Polyp (SSA/P), 10 other], 753 were adenomas (717 tubular, 26 tubulovillous, 10 serrated), and 2 were invasive cancers.

Relationship between endoscopic diagnosis using the NICE classification and pathological diagnosis

Among the 2 groups divided based on polyp size (diminutive and small), we detected 681 diminutive polyps in 402 patients and 197 small polyps in 151 patients. The 681 diminutive polyps consisted of 105 non-neoplastic polyps, 557 low-grade adenomas, 18 high-grade adenomas or intramucosal/SM scanty invasive carcinomas, and 1 SM-d carcinoma. Additionally, the 197 small polyps consisted of 18 non-neoplastic polyps, 154 low-grade adenomas, 24 high-grade adenomas or intramucosal/SM scanty invasive carcinomas, and 1 SM-d carcinoma. The optical features of invasive cancer could

Table 1 Narrow-band imaging International Colorectal Endoscopic Classification[1]

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures[2]	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels[2]	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic	Adenoma[3]	Deep submucosal invasive cancer
Treatment	Follow up	Polypectomy/EMR/ESD	Surgical operation

[1]Can be applied using colonoscopes with or without optical (zoom) magnification; [2]These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening; [3]Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (*e.g.*, depressed area).

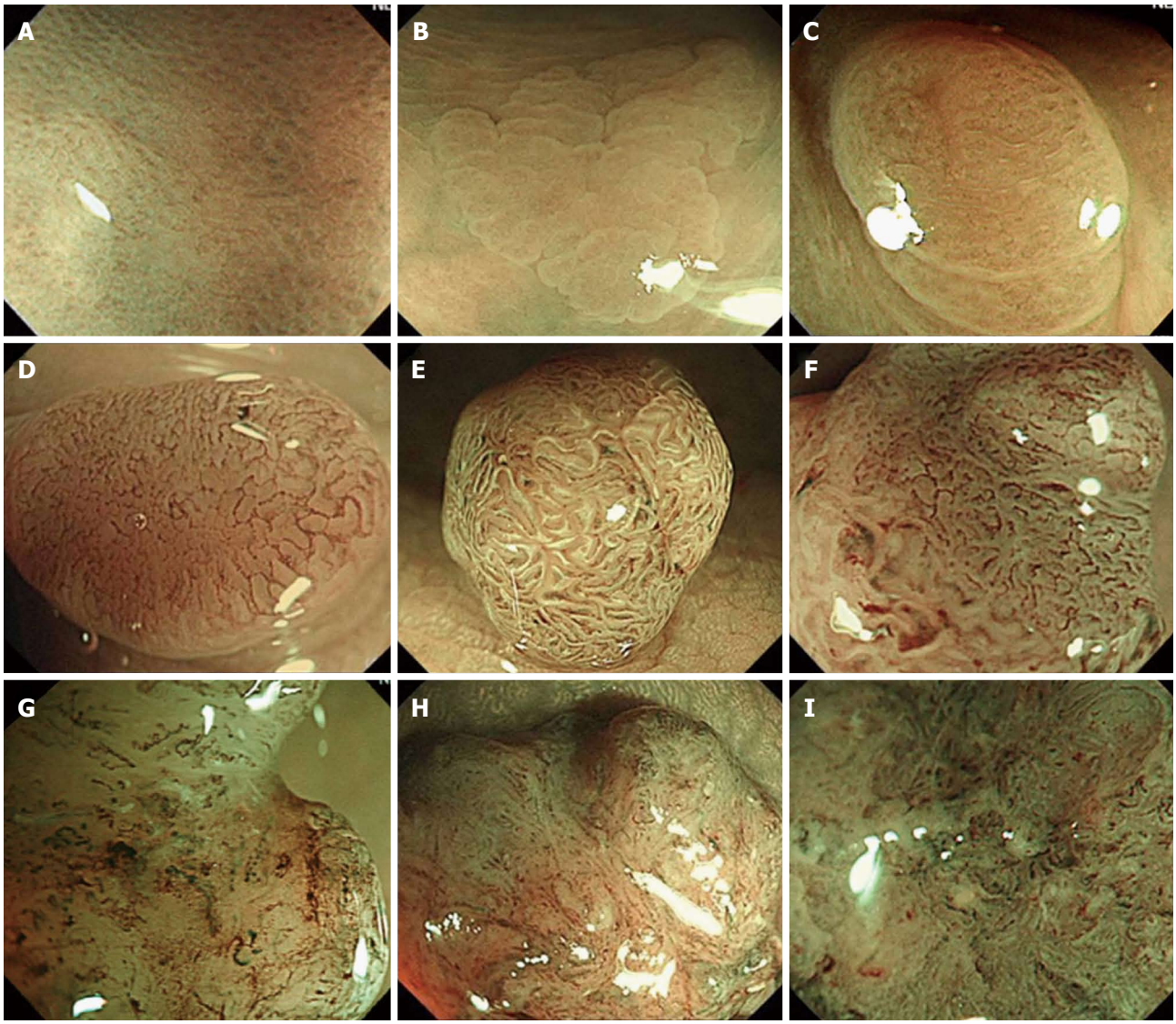

Figure 1 Endoscopic findings of narrow-band imaging observation with magnifying endoscopy. A-C: Lesions classified as NICE type 1; D-F: Lesions classified as NICE type 2; G-I: Lesions classified as NICE type 3.

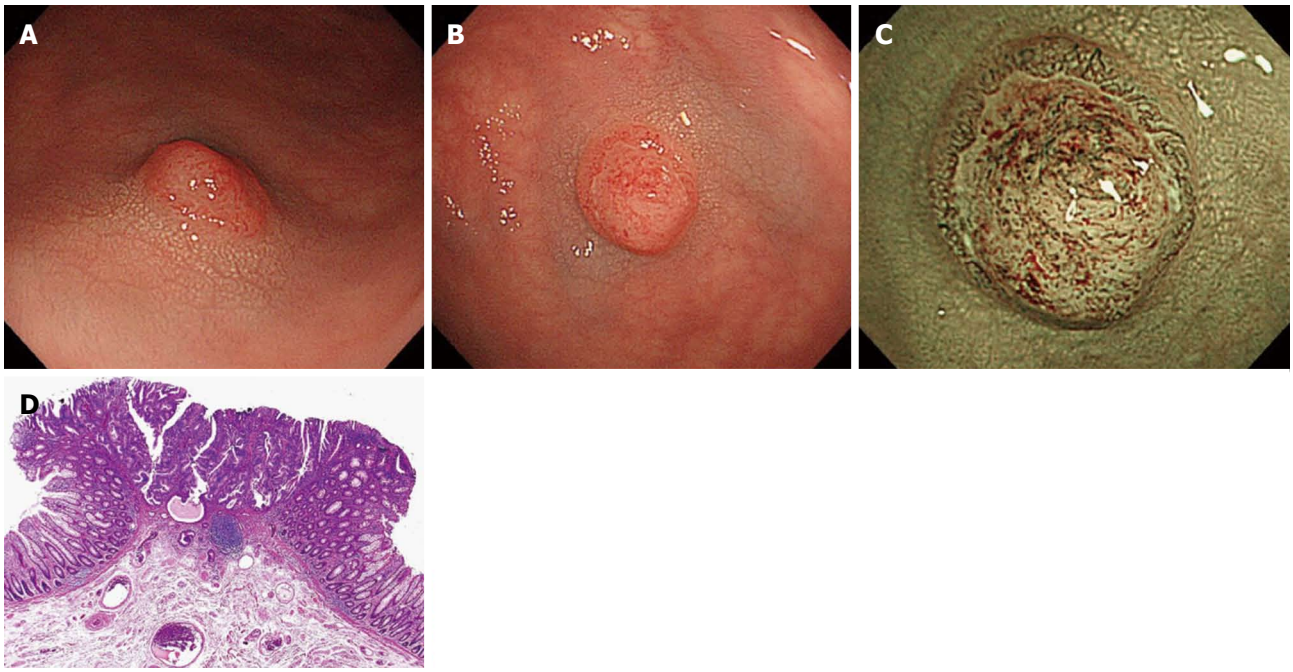

Figure 2 Invasive cancer 1 (S/C, 4 mm, Ⅱa + Ⅱc, Depressed type with NICE type 3). A and B: 0-IIa+IIc lesion was shown in sigmoid colon; C: NBI-magnifying endoscopy showed the feature classified as NICE type 3; D: Pathological diagnosis was well differentiated tubular adenocarcinoma, pSM-M, ly(+), v(-), budding grade 0-1.

be diagnosed as NICE type 3 endoscopically (Figures 2 and 3).

DISCUSSION

Morson[8] described the adenoma-carcinoma sequence in detail, which led to recognition among clinicians worldwide of the course of progression from adenomas to colorectal cancers. Removal of all adenomatous polyps during colonoscopy has been standardized worldwide. As the NPS demonstrated that removal of all adenomatous polyps could significantly reduce colorectal cancer incidence and mortality[1]. At present, it is routine practice to retrieve polyps for pathological evaluation because the accuracy of diagnosis to distinguish non-neoplastic from neoplastic colorectal lesions under observation with white light is not high and usually has a limit of 59% to 84%[9-14].

Image-enhanced endoscopy including NBI was introduced in 2006 and its use has since spread widely and rapidly worldwide, which contributed to improved diagnostic precision even without the use of magnification[15]. Furthermore, the introduction of a concept called the "confidence level" has further improved diagnostic precision.

According to this concept, cases are classified as high confidence (HC) or low confidence (LC), based on the degree of diagnostic certainty. It has already been proven that diagnostic precision is enhanced when only HC cases are subjected to endoscopic diagnosis[2,3]. It was reported that the accuracy rate of diagnosis to distinguish non-neoplastic from neoplastic colorectal lesions improved over 90% in 2009 at academic centers in the United Kingdom and United States through the use of NBI (non-magnifying) for HC cases. In other words, the accuracy of endoscopic diagnosis with HC can be comparable to that of pathological diagnosis. Recently, the "resect and discard" policy was advocated[2,3]. According to this strategy, a hyperplastic polyp in recto-sigmoid colon would be left to reduce the risk of polypectomy, and diminutive or small adenomas would be resected and discarded so as to eliminate the cost of pathological examination. However, discarding polyps without performing histology increases the risk of failing to detect diminutive and small colorectal invasive cancers, which would otherwise be received surgery, and if a recto-sigmoid polyp is left *in situ*, there is a risk of leaving behind a neoplastic lesion if the diagnosis is incorrect.

In the present study, among 878 polyps less than 1 cm in diameter, 2 SM-d carcinomas were identified (Tables 2 and 3). One had a diameter of 4 mm and the other, 6 mm. Both were in the sigmoid colon, with the shape of Ⅱa + Ⅱc, depressed type, and had optical features of invasive carcinoma classified as NICE type 3. Consequently, these 2 patients received adequate surgical treatment (Figures 2 and 3). Additionally, we diagnosed 53 diminutive and 21 small polyps classified as NICE type 1, meaning that they were non-neoplastic and would, according to the "resect and discard" strategy, be left *in situ* if located in the recto-sigmoid colon (Table 3). Of these polyps, 11 diminutive polyps and 9 small polyps were adenomas. The rate of false diagnosis was not low, presumably because the study was not prospective and cases included not only HC cases but also LC cases. Nonetheless, all of the adenomas diagnosed as

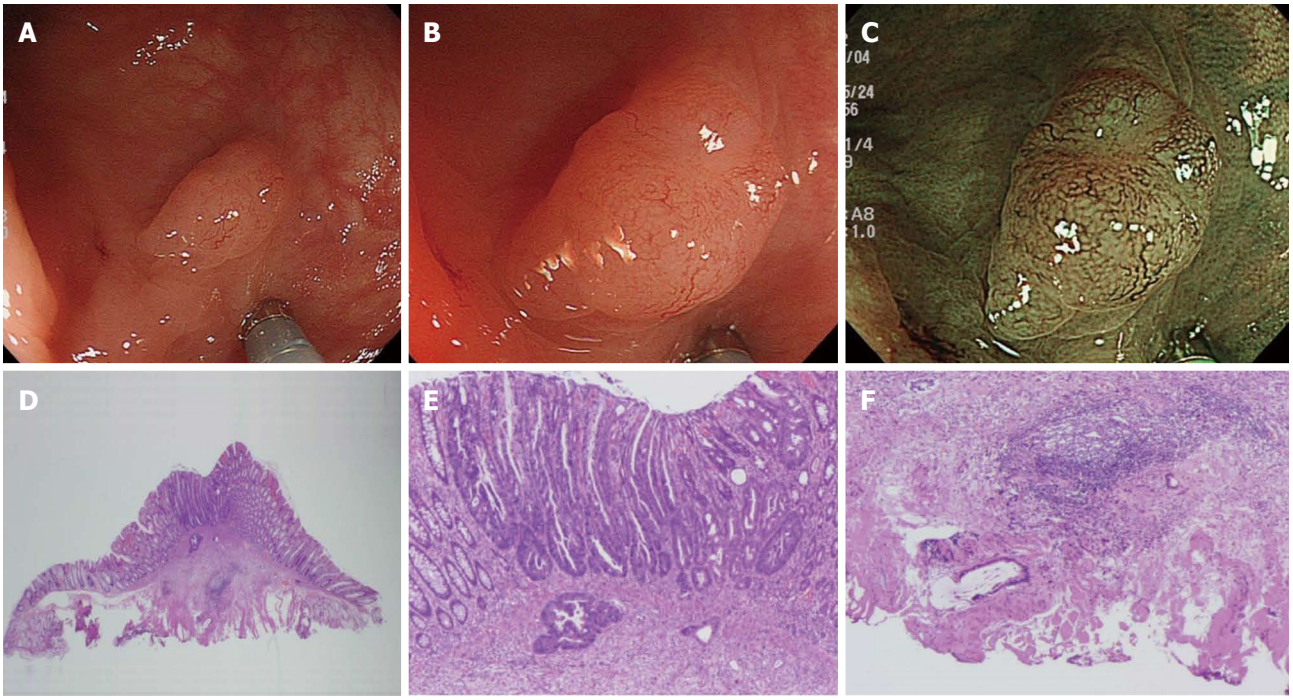

Figure 3 Invasive cancer 2 (S/C, 6 mm, Ⅱa + Ⅱc, Depressed type with NICE type 3). A and B: 0-Ⅱa + Ⅱc lesion was shown in sigmoid colon; C: NBI-magnifying endoscopy showed the feature classified as NICE type 3; D-F: Pathological diagnosis was well differentiated tubular adenocarcinoma with scirrhous growth, pSM-M, pVM(+), ly(+), v(+), budding grade 2-3.

Table 2 Clinicopathological feature

Total patient	468
Male/female	290/178
Mean age	66.3 (32-97, SD:)
Polyps	878
Mean size (mm)	4.7 (1-9, SD:)
Location (right side/left side)	542/336
Shape (pedunculated/sessile/flat/depressed)	12/274/590/2
Histology	
Non-neoplastic	123 (HP:100, SSA/P:13, other:10)
Adenoma	753 (TA:717, TVA:26, SA:10)
Grade (low/high)	711/42
Invasive cancer	2

HP: Hyperplastic polyp; SSA/P: Sessile serrated adenoma/polyp; TA: Tubular adenoma; TVA: Tubulovillous adenoma; SA: Serrated adenoma.

Table 3 Pathological evaluation using NICE classification

NICE classification	Non-neoplastic	Adenoma (low/high)	Invasive cancer
	Diminutive/small	Diminutive/small	Diminutive/small
NICE 1	42/12	11 (11/0)/9 (9/0)	0/0
NICE 2	63/6	564 (546/18) /169 (145/24)	0/0
NICE 3	0/0	0/0	1/1

NICE: NBI international colorectal endoscopic; Diminutive: 1-5 mm in diameter; Small: 6-9 mm in diameter.

NICE type 1 were adenomas with low-grade rather than high-grade atypia. The present data might suggest that the risk of failing to detect diminutive and small invasive colorectal cancers and that of leaving high-grade adenomas or intramucosal/SM scanty invasive carcinomas *in situ* with the "resect and discard" strategy could be avoided through the use of NBI observation with NICE classification and a magnifying endoscope.

The present study had some limitations. This was a single-center retrospective study and confidence levels were not determined. Further prospective research is required to validate the reliability of using the NICE classification with a magnifying endoscope in real-time colonoscopy.

In conclusion, the risk of failing to detect diminutive and small invasive colorectal cancers with the "resect and discard" strategy might be prevented by employing NICE classification under NBI magnification.

COMMENTS

Background

The "resect and discard" strategy offers costs savings benefits because it does not involve histological evaluation of tissue specimens; however, when discarding polyps without evaluating them histologically there is a risk of failure to detect invasive colorectal cancer.

Research frontiers

Recently, the NICE classification was proposed as a valid tool for not only differentiating hyperplastic from adenomatous polyps, but also predicting SM-d carcinomas in colorectal tumors. In the present study the authors aimed to assess the risk of failing to detect diminutive and small colorectal cancers in real-time using the "resect and discard" policy with NICE classification under narrow-band imaging (NBI) magnification.

Innovations and breakthroughs

Previous studies about the "resect and discard" strategy have reported that *in-vivo* optical diagnosis with high-definition white light followed by NBI without

magnification and chromoendoscopy seemed to be acceptable to assess polyp histopathology and future surveillance intervals. In the present study the authors innovated NICE classification and magnifying endoscopy to predict simply SM-d carcinomas among diminutive or small colorectal polyps.

Applications

The present data might suggest that the risk of failing to detect diminutive and small invasive colorectal cancers and that of leaving high-grade adenomas or intramucosal/SM scanty invasive carcinomas *in situ* with the "resect and discard" strategy might be prevented by employing NICE classification under NBI magnification.

Terminology

NICE classification is very simple and based on 3 characteristics including: (1) lesion color; (2) microvascular architecture; and (3) surface pattern, which consists of 3 types as shown in Table 1 and Figure 1.

Peer review

The paper proposes the "resect and discard" strategy of dimunitive and small polyps according their endoscopic features using NBI colonoscopes in conjunction with the NICE classification system.

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P- Reviewer: Karagiannis JA, Parsak C **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Zhang DN

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v6.i12.606

World J Gastrointest Endosc 2014 December 16; 6(12): 606-611
ISSN 1948-5190 (online)

CLINICAL TRIALS STUDY

Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy

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Author contributions: Shah H planned the study protocol and main write up of the article with screening of patients and assessing the bowel preparation; Desai D helped in write up of the article and screening of patients; Samant H and Davavala S helped in enrolling patients for the study and screening them; Joshi A, Gupta T and Abraham P valuable contribution for patient enrollment, screening and editing the article.

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Received: May 15, 2014 Revised: September 11, 2014
Accepted: October 31, 2014
Published online: December 16, 2014

Abstract

AIM: To compare (using the Ottawa Bowel Preparation Scale) the efficacy of split-dose *vs* morning administration of polyethylene glycol solution for colon cleansing in patients undergoing colonoscopy, and to assess the optimal preparation-to-colonoscopy interval.

METHODS: Single-centre, prospective, randomized, investigator-blind stud in an academic tertiary-care centre. Two hundred patients requiring elective colonoscopy were assigned to receive one of the two preparation regimens (split *vs* morning) prior to colonoscopy. Main outcome measurements were bowel preparation quality and patient tolerability.

RESULTS: Split-dose regimen resulted in better bowel preparation compared to morning regimen [Ottawa score mean 5.52 (SD 1.23) *vs* 6.02 (1.34); $P = 0.017$]. On subgroup analysis, for afternoon procedures, both the preparations were equally effective ($P = 0.756$). There was no difference in tolerability and compliance between the two regimens.

CONCLUSION: Overall, previous evening - same morning split-dosing regimen results in better bowel cleansing for colonoscopy compared to morning preparation. For afternoon procedures, both schedules are equally effective; morning preparation may be more convenient to the patient.

Key words: Bowel preparation; Colonoscopy; Morning preparation; Split dose preparation; Preparation to colonoscopy interval

Core tip: Split bowel reparation compared to single dose morning preparation resulted in a better bowel cleansing using the Ottawa Bowel Preparation Scale. The average score (± SD) using the Ottawa Scale was 6.02 ± 1.34 when morning preparation was given and 5.52 ± 1.23 when split preparation was given ($P = 0.017$). However, there was no statistical difference in the mean Ottawa score when the procedures were done in the afternoon with either the morning or the split preparation (6.09 *vs* 5.94, $P = 0.756$). Hence, AM only dosing is as effective as split dosing for patients scheduled for a colonoscopy in the afternoon.

Shah H, Desai D, Samant H, Davavala S, Joshi A, Gupta T, Abraham P. Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2014; 6(12): 606-611 Available from: URL: http://www.wjgnet.com/1948-5190/full/

v6/i12/606.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.606

INTRODUCTION

Successful completion of colonoscopy depends to a large extent on the quality of bowel preparation[1,2]. Poorly visualized mucosa leads to missed diagnoses and increases colonoscopic risk[3-5]. Even a small amount of residual stool can obscure small lesions such as angiodysplasia[5].

Bowel preparation has evolved from previous evening regimen to split dose regimen. Traditional colon preparation involves the unpleasant task of drinking a large volume of a cleansing solution the evening before the procedure. One way to increase tolerability and patient adherence is to split the dose so that the patient takes half the solution the evening before colonoscopy and the other half in the morning, usually about 4 to 5 h before the scheduled time of the procedure[6,7].

Prior studies have demonstrated that split dosing not only to improves patient acceptability, but also cleans the colon better[8]. Of 13 prospective, randomized studies done previously, 12 showed superior cleansing when whole or part of the bowel preparation was given in the morning of the scheduled colonoscopy[9-21].

However colonoscopies are often scheduled in the afternoon, and split dosing may not leave a clean colon by afternoon. A recent study by Matro *et al*[22] showing equal cleansing efficacy and tolerability of a morning dosing and split preparation when procedures are slated for the afternoon; this study did not include procedures scheduled in the morning.

The quality of bowel cleansing is generally assessed by the quantity of solid or liquid stool in the lumen. An adequate colonic examination is one that allows confidence that mass lesions other than small (< 5 mm) polyps not to be obscured by the preparation[23].

The primary aim of this study was to evaluate the efficacy of colon cleansing in patients undergoing colonoscopy, comparing the modality of administration, *i.e.*, split (previous eveningsame morning) *vs* morning-only dose, using the Ottawa Bowel Preparation Scale (Ottawa Scale)[24]. We also assessed how the time interval between the last dose of bowel preparation and the start of colonoscopy, *i.e.*, the preparation-to-colonoscopy (PC) interval, affects the quality of bowel preparation. The secondary aim was to study patient compliance and tolerability to the two preparation regimens and the willingness to repeat the bowel preparation in future if required.

MATERIALS AND METHODS

Patients seen in the outpatient clinic of our department as well as hospitalized patients who required elective colonoscopy were screened for enrolment in the study. Exclusion criteria included patients under 18 years of age, presence of severe renal impairment (creatinine clearance < 30 mL/min) or patients on haemodialysis, pregnant or lactating women, severe congestive heart failure (NYHA Ⅲ or Ⅳ), history of bowel obstruction or resection, known allergies to polyethylene glycol (PEG), and refusal of consent for the study. Patients who were inconvenienced by the timing of bowel preparation were also excluded. Approval from the hospital's ethics committee was obtained. Written, informed consent was obtained from each patient.

Patients were provided written instructions in a sealed opaque envelope, for either of the bowel preparations, by their gastroenterologists who were blinded to the content of the envelope. The envelopes were randomized in blocks of five (using a computer-generated random numbers table) by an independent study assistant who kept the randomization key under lock until the inclusion of the last patient. Investigator and colonoscopist were blinded to group allocation.

Bowel preparation

All patients were instructed to adhere to a liquid diet the day before their colonoscopy, and only clear liquids orally after midnight until the procedure time. The morning preparation group was instructed to consume one packet of PEG dissolved in 2 L of water on the morning of the colonoscopy (between 5 am and 7 am). The split-dose group was instructed to dissolve one packet of PEG in 2 L of water and consume one-half of this the evening before the day of the colonoscopy (between 6 pm and 7 pm) and the other half on the morning of the procedure (between 6 am and 7 am).

Patients were advised not to discuss their bowel preparation with their endoscopist but to contact the study assistant or the receiving nurse if questions arose. A mechanism was established to address patient concerns and issues of safety, without unblinding the endoscopist. They were given a questionnaire to be completed once their bowel preparation was finished and before coming to the hospital for the colonoscopy. The questionnaire included details about the tolerability of the regimen, compliance with the instructions for bowel preparation and diet, the amount of preparation taken, and completion time of the last PEG dose. Drinking at least 75% of the preparation volume was regarded as proper amount of PEG taken for bowel preparation. The following data were also collected: age, sex, indication for the procedure, history of abdominal or gynaecologic surgery, history of constipation, and other co-morbidities including diabetes, hypertension, and renal failure.

Colonoscopy

Colonoscopies were performed with the patients under conscious sedation by either a gastroenterology fellow or a consultant gastroenterologist. All colonoscopies were done between 11 am and 4 pm (morning sessions between 11 am and 1 pm, afternoon sessions between 1 pm and 4 pm). Time of completion of the last PEG dose and colonoscopy starting time were recorded, and

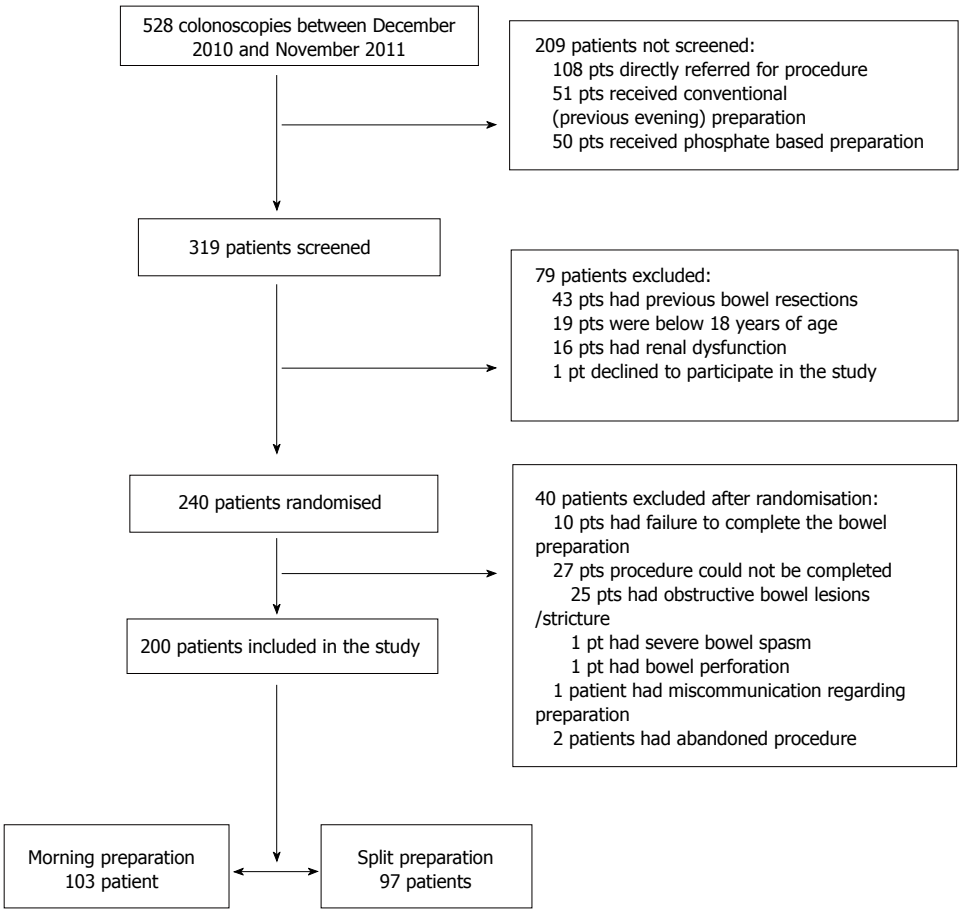

Figure 1 Study design: Group Randomisation.

the PC interval was calculated. A minimum of 4 h was kept between the completion of the last PEG dose and the start of colonoscopy for all patients.

A combination of intravenous fentanyl 50 mcg and midazolam 2 mg was used for sedation in patients in whom there was no contraindication; half the dose was used in patients over the age of 60 years. Additional sedation was used if required and permissible. Pulse, blood pressure, and oxygen saturation were measured in all patients before, during and after the procedure.

Bowel cleansing was evaluated by using the Ottawa Bowel Preparation Scale[24]. This scale assesses cleanliness and fluid volume separately. Cleanliness was assessed separately for the right colon (caecum, ascending), mid colon (transverse, descending), and the rectosigmoid on a 5-point scale (no liquid = 0, minimal liquid, no suctioning required = 1, suction required to see mucosa = 2, wash and suction = 3, solid stool, not washable = 4). Fluid quantity was rated from 0 to 2 for the entire colon (minimal = 0, moderate = 1, large = 2). The Ottawa Scale scores range from 0 (perfect) to 14 (completely unprepared colon). An excellent preparation would score 0 to 2; a good preparation, 3 to 5; and scores higher than 5 would indicate progressively worsening bowel preparation. A completely unprepared colon would score 11 to 14, depending on the amount of colonic fluid. The quality of preparation was assessed at the time of insertion of the colonoscope before any cleansing maneuvers. Each patient's colonoscopy was recorded on a DVD; the bowel-preparation quality was rated by a single investigator who was blinded to the type of preparation, and the results recorded on a standardized form.

Statistical analysis

On the basis of data from previous studies[20-22], a sample size of 200 patients was estimated to give an 80% power at a two-sided alpha of 0.05% to detect a 15% difference in the Ottawa bowel preparation quality scale. Bowel preparation scores measured by the Ottawa Scale were compared between the morning and split-dose groups using the Mann-Whitney *U* test. Pearson χ^2 test and continuity correction was used for comparing proportions in the two groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In this prospective, randomized, investigator-blinded study, we enrolled 200 patients (mean age 51.8 years, SD 15.9, range 18-88; 121 men) between December 2010 and November 2011. A total of 528 colonoscopies were done during this period. Of these, 319 patients were screened for inclusion in the study. Screening was not possible

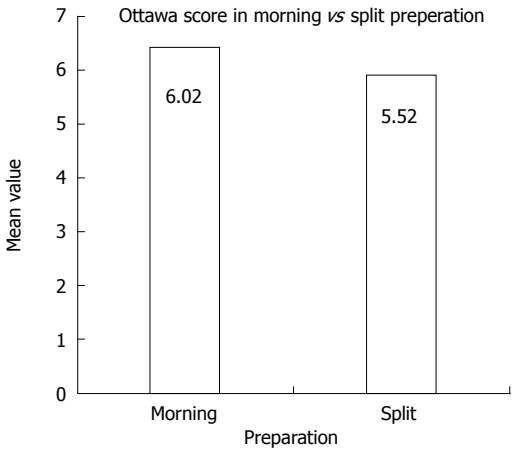

Figure 2 Comparison of morning and split preparation using Ottawa score.

in the remaining 209 patients-108 patients were directly referred for colonoscopy without being randomized, 51 were given the conventional previous-evening bowel preparation, and 50 took another bowel-preparation solution as advised by their referring physician. Of the 319 patients screened, 240 were randomized; 79 patients were excluded as they did not meet the inclusion criteria: previous bowel surgeries (n = 43), below age 18 years (19), renal dysfunction or on haemodialysis (16), and refusal of consent (1).

Of the 240 patients randomized, 40 were excluded: failure to complete bowel preparation as advised (n = 10; 6 in morning and 4 in split dose regimen); miscommunication regarding bowel preparation (1); inability to complete colonoscopy due to bowel lesion/stricture (25), spasm (1) and perforation (1). Two patients had extremely poor bowel preparation (both had taken morning preparation) and hence colonoscopy was abandoned and they were given a repeat bowel preparation.

Cecal intubation rate was 99.5% in our study. Only patients who had a complete colon examination from anal verge up to the cecum were included in the analysis. Of 200 such patients (109 outpatients, 91 inpatients), 103 received morning preparation and 97 received the split preparation (Figure 1). Total 135 patients underwent endoscopies in the morning (70 from morning preparation and 65 from split preparation). Both groups were comparable in terms of demographic data (62 males in morning preparation and 59 males in split preparation, median age = 53 years in both groups) and indications for colonoscopy.

Quality of bowel preparation

The split preparation had better bowel efficacy compared to the morning preparation. Overall, 88 (44%) patients had Ottawa score 5 or less indicating good bowel preparation. 93 (46.5%) had average bowel preparation with score 6 and 7, and 19 (9.5%) patients had poor bowel preparation with score above 8. The mean Ottawa Scale score (SD) was 6.02 (1.34) with the morning preparation and 5.52 (1.23) with split preparation (P = 0.017) (Figure 2). With morning colonoscopy (11 am-1 pm), the mean Ottawa score was 5.99 and 5.31 (P = 0.007) for the morning and split preparations, respectively. With afternoon colonoscopy, the corresponding scores were 6.09 and 5.94 (P = 0.756), respectively.

PC interval

A gap of at least 4 h was kept for every patient between the last preparation intake and the time of colonoscopy. Afternoon colonoscopies with PC interval > 6 h had poor bowel preparation (Ottawa score 5.66) compared to morning colonoscopies with PC interval between 4 and 6 h (6.02; P = 0.075).

Tolerability of the preparation and sleep disturbance

Nausea was complained of by 29.1% of patients with the morning preparation and 19.6% with split preparation (P = 0.161), abdominal discomfort by 9.7% and 13.4%, (P = 0.551), vomiting by 10.7% and 11.3% (P = 1.0), bloating by 12.6% and 9.3% (P = 0.597), and headache, dizziness and uneasiness by 4.9% and 4.1%, respectively (P = 1.0). Sleep was disturbed in 8 (7.8%) patients receiving the morning preparation and in 14 (14.4%) patients receiving the split preparation (P = 0.201). No patient experienced inconvenience while travelling.

DISCUSSION

Traditionally, the entire bowel-cleansing preparation solution is given in the evening prior to colonoscopy. In order to avoid sleep disturbance, it has to be given early in the evening. Alternatively, the preparation solution can be taken in a split dose, 8-12 h apart. Studies have shown that ingesting at least a part of the purgative on the day of colonoscopy and coordinating the final dose of purgative with the start time of colonoscopy is more likely to result in adequate colon cleansing[11,25]. Generally, this is accomplished by splitting the purgative between the evening prior and the morning of colonoscopy.

Previous studies have shown that the split preparation is better than the conventional previous-evening preparation in terms of bowel preparation quality and patient compliance[14,17,18,25,26]. The split-dose option is also endorsed by the American College of Gastroenterology and is considered an optimal choice for colonoscopy[27]. However, there have been few studies comparing split preparation to same-day morning preparation, which may be more convenient to patients as it does not interfere with common office schedules. We have shown earlier that same-morning preparation was better than previous-evening preparation[20]. In the present study we compared split dose with same-morning preparation.

In this study, split dosing resulted in better bowel cleansing than the same-morning preparation, both overall and when colonoscopy was performed in the morning. However, there was no difference in the mean

Ottawa score when colonoscopies were done in the afternoon. For patients scheduled for a colonoscopy in the afternoon, either of the preparation is comparable. The advantage of the morning preparation is it interferes less with the patient's routines and work schedules; patients often complain about trouble sleeping after taking the evening preparation.

A PC interval of 4 to 6 h resulted in better bowel preparation compared to one greater than 6 h. When patients were scheduled for the afternoon list, an interval between preparation and procedure greater than 6 h resulted in inferior bowel preparation, although this was not statistically significant. A long interval results in thick secretions emptying out of the small intestine and obscuring the caecum and ascending colon at the time of colonoscopy.

Seo *et al*[28] evaluated 366 consecutive outpatients undergoing colonoscopy using the split preparation; colonoscopies with PC interval 3 to 5 h had the best bowel preparation quality. Matro *et al*[22] compared the efficacy and tolerability of morning-only PEG to split-dose PEG for afternoon colonoscopy, and found both equivalent with respect to cleansing efficacy and polyp detection. Morning-only preparation was associated with lower incidence of abdominal pain, superior sleep quality, and less interference with work day prior to colonoscopy. While conventionally colonoscopies are performed in the morning, linking the administration of the preparation to the time of the procedure for both morning-only and split dosing may make late morning and afternoon colonoscopy equally attractive to patients.

In our study, there was no difference in tolerability between the morning and split regimens. Both regimens were equally well tolerated, with most patients willing to repeat the preparation in the future if the need arises.

In conclusion, split evening-morning dosing is superior to morning-only dosing for colon cleansing prior to colonoscopy if the procedure is slated in the morning; for afternoon colonoscopy, morning-only preparation is as effective. Optimal colon cleansing requires purgative administration close to the time of colonoscopy. For patients scheduled for colonoscopy in afternoon, it may be convenient to take the preparation in morning so that PC interval is minimized.

COMMENTS

Background

There is no standard recommendation regarding the timing of colonoscopy preparation. Different regimens are mentioned in literature. Traditionally, the entire preparatory solution is given in the evening, a day prior to the procedure. Alternatively, the preparatory solution can be taken in a split dose, 8-12 h apart. Studies have shown that ingesting at least a part of the purgative on the day of colonoscopy and coordinating the final dose of purgative with the start time of colonoscopy is more likely to result in adequate colon cleansing. Generally, this is accomplished by splitting the purgative between the evening prior and the morning of colonoscopy. Previous studies have proved that the split preparation is better than the conventional previous evening preparation in terms of bowel preparation quality and patient compliance. The split dose option is also endorsed by the American College of Gastroenterology and is considered an optimal choice for colonoscopy. But there have been very few studies comparing split preparation to same day morning preparation, which is more relevant to current clinical practice. What people looked at was can people administer the colon preparation the same day and get equal results? Is there a better way for bowel preparation without inconveniencing the patient? This rationale for the study was to compare the quality of bowel preparation using the same morning *vs* split regimens and also assess the importance of preparation-to-colonoscopy (PC) interval. The primary endpoint was whole colon preparation adequacy.

Research frontiers

Though there are several factors implicated in successful completion of a colonoscopy, quality of bowel preparation and timing of colonoscopy are considered two modifiable factors to improve successful completion. Improving the quality of colonoscopy is a major initiative of many digestive disease organizations. Various studies are ongoing to assess how the time interval between the last dose of bowel preparation and the start of colonoscopy, *i.e.*, the PC interval, affects the quality of bowel preparation and to determine the optimal PC interval for satisfactory bowel preparation.

Innovations and breakthroughs

Previous studies have proved that the split preparation is better than the conventional previous evening preparation in terms of bowel preparation quality and patient compliance. However, in this study there was no difference in the quality of bowel preparation for patients undergoing colonoscopy in afternoon with either the split or the same day morning preparation. Hence, same day bowel preparation should become a new standard for afternoon colonoscopy.

Applications

This study expands the options for patients by demonstrating that ingestion of polyethylene glycol preparation entirely on the day of colonoscopy is as good as a split dose schedule for an afternoon procedure.

Terminology

Split preparation: Where the patient takes half the laxative prescription the evening before colonoscopy and the other half in the morning of the scheduled procedure.

Peer review

The article entitled "Comparison of split-dosing *vs* non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy" by Shah *et al* describes a study comparing the effect of morning-only and split bowel preparation of PEG solutions on bowel cleansing, for both morning and afternoon colonoscopies. Overall this study is timely and interesting to the readership.

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P- Reviewer: Damin DC, Gioux S, Souza JLS, Wu B
S- Editor: Song XX **L- Editor**: A **E- Editor**: Zhang DN

World Journal of Gastrointestinal Endoscopy

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v6.i12.612

World J Gastrointest Endosc 2014 December 16; 6(12): 612-619
ISSN 1948-5190 (online)

PROSPECTIVE STUDY

Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding

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Supported by Patients or their insurance for capsule endoscopy; by NIMTS General Hospital

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Received: August 3, 2014 Revised: November 5, 2014
Accepted: November 17, 2014
Published online: December 16, 2014

Abstract

AIM: To determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer and define the significance of those lesions.

METHODS: In our prospective study, 60 consecutive elderly patients with upper gastrointestinal bleeding from a peptic ulceration (cases) and 60 matched patients with a non-bleeding peptic ulcer (controls) underwent small bowel capsule endoscopy, after a negative colonoscopy (compulsory in our institution). Controls were evaluated for non-bleeding indications. Known or suspected chronic inflammatory conditions and medication that could harm the gut were excluded. During capsule endoscopy, small bowel ulcerative lesions were counted thoroughly and classified according to Graham classification. Other small bowel lesions were also recorded. Peptic ulcer bleeding was controlled endoscopically, when adequate, proton pump inhibitors were started in both cases and controls, and *Helicobacter pylori* eradicated whenever present. Both cases and controls were followed up for a year. In case of bleeding recurrence upper gastrointestinal endoscopy was repeated and whenever it remained unexplained it was followed by repeat colonoscopy and capsule endoscopy.

RESULTS: Forty (67%) cases and 18 (30%) controls presented small bowel erosions (P = 0.0001), while 22 (37%) cases and 4 (8%) controls presented small bowel ulcers (P < 0.0001). Among non-steroidal anti-inflammatory drug (NSAID) consumers, 39 (95%) cases and 17 (33%) controls presented small bowel erosions (P < 0.0001), while 22 (55%) cases and 4 (10%) controls presented small bowel ulcers (P < 0.0001). Small bowel ulcerative lesions were infrequent among patients not consuming NSAIDs. Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with small bowel ulcerative lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). Cases with small bowel ulcers necessitate more units of packed red blood cells. During their hospitalization, 6 (27%) cases with small bowel ulcers presented bleeding recurrence most possibly attributed to small bowel ulcers, nevertheless 30-d mortality was zero. Presence of chronic obstructive lung disease and diabetes was related with unexplained recurrence of hemorrhage in logistic regression analysis, while absence of small bowel ulcers was protective (relative risk 0.13, P = 0.05).

CONCLUSION: Among NSAID consumers, more bleeders than non-bleeders with peptic ulcers present small bowel ulcers; lesions related to more severe bleeding and unexplained episodes of bleeding recurrence.

Key words: Non-steroidal anti-inflammatory drugs; Aspirin; Wireless capsule endoscopy; Small bowel ulcerative lesions; Peptic ulcer bleeding

Core tip: Non-steroidal anti-inflammatory drugs (NSAIDs) can frequently cause small bowel ulcerative lesions. In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs also presented small bowel erosions and 55% small bowel ulcers. Small bowel ulcerative lesions were 3 times less frequent in patients with a non-bleeding peptic ulcer consuming NSAIDs, and infrequent among patients with a peptic ulcer not receiving NSAIDs. Small bowel ulcers in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Moreover, they could be incriminated for unexplained bleeding recurrence despite successful peptic ulcer hemostasis.

Tsibouris P, Kalantzis C, Apostolopoulos P, Zalonis A, Isaacs PET, Hendrickse M, Alexandrakis G. Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding. *World J Gastrointest Endosc* 2014; 6(12): 612-619 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/612.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.612

INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) therapy reduces inflammation and pain very effectively[1], whilst low-dose aspirin is a common antithrombotic drug[2]. Benefits from NSAID use are offset by potentially life-threatening gastrointestinal complications[3-5]. NSAIDs can cause functional and structural small intestinal abnormalities[4,5]. The later could be accessed by either double-balloon[6] or capsule endoscopy (WCE)[1].

WCE identified small bowel mucosal damage (mucosal breaks, reddened folds, petechiae and denuded mucosa) in 50%-70% of healthy volunteers after a short course of NSAIDs and even more lesions in chronic NSAID consumers[1,7,8]. On the contrary mucosal damage was present only in 10% of subjects not exposed to NSAIDs[1]. Although small bowel mucosal lesions are frequent, they rarely produce small and large bowel complications[9]. Less than 1% of overt or obscure gastrointestinal bleeding cases can be attributed to small bowel ulcerative lesions[10]. Type of NSAID treatment (aspirin, non-aspirin NSAIDs) and patient age can increase the risk for a bleeding episode[11]. The role of a concurrent peptic ulcer is rather unknown.

In a small study, 90% of patients with a non-bleeding gastric ulcer receiving low dose aspirin also presented small bowel mucosal lesions[12]. A small pilot study in our department provided an indication that small bowel ulcerative lesions are even more frequent in peptic ulcer bleeders[13].

Our primary end-point was to determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer bleeding compared to those with non-bleeding ulcers. While our secondary end-points were to determine: (1) whether NSAID use affects the frequency of small bowel lesions and (2) whether presence of small bowel lesions affects the severity of the bleeding episode and its' outcome.

MATERIALS AND METHODS

Patients-data

Our study was a prospective one. 60 consecutive patients older than 18 years, admitted in NIMTS Hospital (Military Insurance Fund Hospital) between the 1/1/2008 and 31/12/2009 with upper gastrointestinal bleeding due to a peptic ulcer entered the study (cases). None had a previous history of iron deficiency anemia. Each case was matched for age, gender, smoking, and alcohol consumption, to a non-bleeding ulcer patient (control) evaluated with WCE, between 1/1/2008 and 31/12/2012 in our department. Controls had WCE performed for chronic diarrhea or unexplained diffuse abdominal pain.

Upper gastrointestinal endoscopy was performed for each case within 24 h from admission and comprised hemostasis for Forrest I a, I b or II a ulcers[14]. For controls upper gastrointestinal endoscopy was performed before WCE study. During entry gastroscopy, *Helicobacter pylori* (*H. pylori*) infection was determined using rapid urease test and histology (haematoxylin-eosin and modified Giemsa). A negative colonoscopy was an inclusion prerequisite for both cases and controls. Colonoscopy was obligatory in our hospital for every case of gastrointestinal bleeding, regarded as alarm symptomatology not with-held by upper-endoscopy findings, because a significant percentage of patients with peptic ulcer might have a colonic pathology as well[15]. No case or control was on proton pump inhibitor or H-2 receptor blocker before the study period. Continuous *iv* infusion of pantoprazole 8 mg/h after a bolus of 40 mg was started after hemostasis for 48 h; switched thereafter to pantoprazole 40 mg *po* o.d. Cases not necessitating hemostasis and controls received pantoprazole 40 mg *po* o.d.

Hemoglobin levels were measured in every case on admission and daily thereafter until discharge. Hemoglobin drop on admission was calculated from a reference level of 14 g/dL.

Exclusion criteria were pregnancy, known or suspected complete or partial stenosis of the small intestine, gastric or intestinal surgery, established delayed gastric emptying or diabetic gastroparesis, history of, or active, malignancy, history of hypersensitivity to proton pump inhibitors and presence of any serious central nervous system, psychiatric, cardiovascular, respiratory, musculoskeletal, or intestinal disease preventing the performance of WCE. We also excluded patients with known or suspected small bowel inflammation, including Crohn's disease, spondyloarthropathy, and seronegative

athritides; patients with celiac disease and patients on medication that influence NSAID enteropathy[16] (biologicals, sulphasalazine, misoprostol, metronidazole and biphosphonates). No case or control had a systemic rheumatic disease or received anticoagulants. Alcohol intake was withheld during the study period.

Actual NSAIDs consumption (including self medication and defaults from prescribed drugs) was accessed before WCE using a life style and medication questionnaire[17]. We validated the questionnaire, applying it to 20 patients before study initiation (k-value = 0.81). Although we intended to record any NSAID consumption, we have considered NSAIDs consumers only those patients who had received even a single dose of NSAIDs the week preceded WCE study. Continuous NSAIDs consumption (both aspirin and non-aspirin) for up to 2 wk was recorded as short term, while longer-term use was considered long-term[1,7,8].

The study protocol has the approval of the Scientific Council of NIMTS Hospital, standing for Ethics Committee of NIMTS Hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). All patients gave and signed written informed consent, before entering the study.

Capsule endoscopy

Both cases and controls underwent WCE within 4 d after upper gastrointestinal endoscopy and colonoscopy. WCE study (Given SB2 video capsule system; Given Imaging Ltd) was performed according to conventional procedures described elsewhere[10] and it was part of the investigation protocol.

Monitoring period was 9 h. A.Z. has initially gone through all videos and defined the second part of the duodenum. Two independent endoscopists (P. T. and C. K) with vast endoscopic experience separately reviewed all videos, starting video reading from the second part of the duodenum. Both had no information on patient clinical characteristics or presence of any gastric or duodenal bulb lesions. In case of investigator disagreement, a third blinded expert (P. A.) reviewed the findings with the purpose of reaching a consensus. Small bowel mucosal lesions were classified according to Graham *et al*[1]: category 0, normal; category 1, petechiae/red spots; category 2, 1-4 ulcerative lesions up to 5 mm (erosions); category 3, > 4 erosions; and category 4, larger ulcerative lesions. Because agreement between the two investigators was almost perfect (k-value = 0.84) for grade-3 and 4 lesions and fair (k-value = 0.28) for scarce red spots and petechiae and because grade-2 lesions could be found in normal subjects[1], we confined the analysis in grade-3 (erosions) and 4 (larger ulcers) lesions. Other pathologic findings, mainly lymphangiectasia, angiodysplasias and polypoid lesions/tumors were also reported.

Patients with any small bowel pathology undergone repeat capsule endoscopy study a year later. In the meanwhile, NSAID use was prevented; *H. pylori* infection eradicated and polypoid/submucosal lesions received relevant treatment.

To overcome relevant biases, both Head of the Department (G. A.), responsible for treatment decision and ward trainee doctors were unaware of WCE report, unless it was decisive to refer for surgical or endoscopic treatment.

Statistical analysis

Student's *t*-test was used to calculate the difference between the means. The chi-square test or Fisher's exact test was used for nonparametric data as appropriate. A $P < 0.05$ was considered to be statistically significant. We performed logistic regression analysis to access risk factors for unexplained bleeding recurrence. We included known risk factors for ulcer bleeding recurrence (old age, male gender, diabetes mellitus, body mass index and presence of chronic obstructive lung disease) as well as a possible risk factor, presence of small bowel ulcers. The magnitude of each association was expressed in terms of odds ratio and the corresponding 95% confidence interval.

Assuming that: (1) two thirds of patients with peptic ulcer consumed NSAIDs; (2) 30% of patients with no bleeding peptic ulcer consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[9]; and (3) 90% of peptic ulcer bleeders, consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[13]: we estimated that a sample size of 30 patients in each patient group was adequate to reach a study power of 90%. We doubled sample size to secure adequate subgroup analysis (aspirin, non-aspirin NSAIDs).

RESULTS

Patients

A duodenal ulcer was found in 38 (63%) cases and as many controls and a gastric ulcer in 32 (53%) cases and an equal number of controls. Both gastric and duodenal ulcers were present in 10 (17%) cases and 10 (17%) controls. 6 (10%) cases had bled from the gastric and 4 (7%) from the duodenal ulcer. Hemostasis was performed in 12 (20%) cases; 8 (13%) with a duodenal and 4 (7%) with a gastric ulcer. Thirty-two (53%) cases and as many controls were receiving NSAIDs short-term ($P = 1.00$), while 8 (13%) cases and as many controls were on NSAIDs long-term ($P = 1.00$). There was no difference between cases and controls in any demographic or disease related characteristic, apart from diffuse abdominal pain that was more frequent among controls (Table 1). No case or control had chronic renal failure, liver failure or cirrhosis and none was receiving anticoagulants.

Findings in capsule endoscopy

Small bowel ulcerative lesions were found in 40 (67%)

Table 1 Demographic and disease related characteristics of bleeders and controls

Characteristic	Patients (n = 60)	Controls (n = 60)	P
Mean age (yr)	75 (SD = 8)	74 (SD = 9)	0.26
Male gender	44 (73%)	44 (73%)	1.00
Active smoking	18 (30%)	18 (30%)	1.00
Alcohol abuse	12 (20%)	12 (20%)	1.00
BMI > 25	36 (60%)	36 (60%)	1.00
NSAIDs consumption	40 (67%)	40 (67%)	1.00
Ischaemic heart disease	20 (33%)	20 (33%)	1.00
Chronic pain	6 (10%)	22 (37%)	0.006
Diabetes melitus	11 (18%)	12 (20%)	0.82
COPD	4 (7%)	4 (7%)	1.00
Low dose aspirin use[1]	22 (37%)	22 (37%)	1.00
Non aspirin NSAIDs use[1]	24 (40%)	24 (40%)	1.00
COX-2 selective use	6 (10%)	6 (10%)	1.00
Non selective NSAIDs use	18 (30%)	18 (30%)	1.00
Clopidogrel co-administration	12 (20%)	12 (20%)	1.00
Gastric passing time (min)	41 (SD = 49)	42 (SD = 57)	0.46
Small bowel passing time (min)	221 (SD = 117)	271 (SD = 117)	0.01
H. pylori positive	37 (60%)	37 (62%)	1.00

[1]Three bleeders and 6 controls received both low-dose aspirin and non-aspirin NSAIDs. SD: Standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs; BMI: Body mass index; COPD: Chronic obstructive lung disease; COX-2 selective use: Cyclooxygenase-2 selective inhibitors.

cases and 18 (30%) controls (P = 0.0001). All of them had erosions (grade-3 lesions), while small bowel ulcers (grade-4 lesions) were found 22 cases (37%) and 4 (8%) controls (P = 0.0001). Small bowel erosions were found in 27 (71%) cases with a duodenal and 20 (62%) with a gastric ulcer (P = 0.45), while small bowel ulcers were found in 16 (42%) cases with a duodenal and 10 (31%) with a gastric ulcer (P = 0.35). Moreover erosions were found in 14 (37%) controls with a duodenal and 9 (28%) with a gastric ulcer (P = 0.44), while small bowel ulcers were found in 3 (8%) controls with a duodenal and 2 (6%) with a gastric ulcer (P = 0.79).

Among NSAID consumers, 39 (98%) cases and 17 (43%) controls presented small bowel ulcerative lesions (P < 0.0001). All of them had small bowel erosions, while small bowel ulcers were present in 22 (55%) cases and 4 (10%) controls (P < 0.0001). Small bowel erosions were found in 26 (96%) cases with a duodenal and 20 (100%) with a gastric ulcer (P = 0.38), while larger ulcerative lesions were found in 16 (100%) cases with a duodenal and 10 (100%) with a gastric ulcer (P = 1.00). Moreover erosions were found in 13 (48%) controls with a duodenal and 9 (45%) with a gastric ulcer (P = 0.83), while larger ulcerative lesions were found in 3 (11%) controls with a duodenal and 2 (10%) with a gastric ulcer (P = 0.90).

There was no difference in small bowel mucosal lesions between cases and controls consuming no NSAIDs (Table 2). All cases and controls with small bowel erosions reporting no NSAID consumption admitted that they had received at least a single NSAID dose more than a week before WCE.

Among NSAID consumers, cases presented more small bowel erosions than controls both in the jejunum and the in the ileum (Table 3).

Small bowel erosions were present in 31 (97%) cases receiving NSAIDs long-term and 8 (100%) short-term

Table 2 Small bowel mucosal lesions found during video capsule endoscopy in both bleeders and controls

Patient group	Cases	Controls	P
All patients	n = 60	n = 60	
Grade 4 lesions	22 (37%)	4 (8%)	0.0001
Grade 3 lesions	40 (67%)	18 (30%)	0.0001
Grade 2 lesions	41 (68%)	21 (35%)	0.0003
Grade 1 lesions	42 (70%)	28 (47%)	0.0100
NSAID consumers	n = 40	n = 40	
Grade 4 lesions	22 (55%)	4 (10%)	< 0.0001
Grade 3 lesions	39 (95%)	17 (33%)	< 0.0001
Grade 2 lesions	40 (100%)	20 (50%)	< 0.0001
Grade 1 lesions	40 (100%)	26 (65%)	< 0.0001
No-NSAID consumers	n = 20	n = 20	
Grade 4 lesions	0	0	
Grade 3 lesions	1 (5%)	1 (5%)	1.00
Grade 2 lesions	1 (5%)	1 (5%)	1.00
Grade 1 lesions	2 (10%)	2 (10%)	1.00

NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 3 Number of mucosal lesions found during video capsule endoscopy in both bleeders and controls consuming non-steroidal anti-inflammatory drugs, after stratification according to the type of non-steroidal anti-inflammatory drug consumed

Patient group	Patients	Controls	P
All patients	n = 40	n = 40	
Jejunum			
Grade 4 lesions	1 (SD = 2)	0.3 (SD = 0.7)	0.02
Grade 3 lesions	10.8 (SD = 4.3)	1 (SD = 0.6)	< 0.0001
Ileum			
Grade 4 lesions	1.1 (SD = 1.9)	0.2 (SD = 0.3)	0.002
Grade 3 lesions	8.1 (SD = 4.8)	1.2 (SD = 2.2)	< 0.0001
Low dose aspirin users	n = 22	n = 22	
Jejunum			
Grade 4 lesions	0.8 (SD = 1.3)	0.2 (SD = 0.4)	0.02
Grade 3 lesions	9.9 (SD = 4.7)	0.8 (SD = 0.5)	< 0.0001
Ileum			
Grade 4 lesions	0.9 (SD = 1.4)	0.1 (SD = 0.3)	0.006
Grade 3 lesions	10.3 (SD = 4.6)	1 (SD = 1.6)	< 0.0001
Non-aspirin NSAID consumers	n = 24	n = 24	
Jejunum			
Grade 4 lesions	1.4 (SD = 2.6)	0.4 (SD = 0.9)	0.04
Grade 3 lesions	11.9 (SD = 3.8)	1.2 (SD = 0.7)	< 0.0001
Ileum			
Grade 4 lesions	1.6 (SD = 2.4)	0.3 (SD = 0.3)	0.02
Grade 3 lesions	7.7 (SD = 4.8)	1.4 (SD = 2.3)	< 0.0001
COX-2 NSAID consumers	n = 6	n = 6	
Jejunum			
Grade 4 lesions	0.3 (SD = 0.6)	0	0.27
Grade 3 lesions	5.7 (SD = 6.7)	0.4 (SD = 1.4)	0.04
Ileum			
Grade 4 lesions	0.7 (SD = 1.2)	0	0.15
Grade 3 lesions	6.7 (SD = 5.7)	0.5 (SD = 0.7)	0.01

NSAIDs: Non-steroidal anti-inflammatory drugs; SD: Standard deviation; COX-2: Cyclooxygenase-2 selective inhibitors.

Table 4 Logistic regression analysis of demographic characteristics and co-morbidities related to a hemorrhage recurrence possibly related to the small bowel

Characteristic	Relative risk	Confidence intervals	*P*
Age	1.03	0.96-1.10	0.40
Male gender	3.63	0.61-21.46	0.15
Body mass index	1.22	0.90-1.63	0.19
Diabetes	2.14	1.35-3.40	0.001
Chronic obstructive lung disease	6.67	1.01-46.3	0.05
Absence of small bowel ulcers	0.13	0.01-0.99	0.05

(P = 0.61), while larger ulcerative lesions were found in 19 (59%) cases consuming NSAIDs long-term and 3 (38%) consuming them short-term (P = 0.27). On the other hand, small bowel erosions were found in 15 (47%) controls consuming NSAIDs long-term and 3 short-term (38%, P = 0.63); while small bowel ulcers were found in 3 (9%) controls consuming NSAIDs long-term and 1 long-term (13%, P = 0.79).

Twenty-four (67%) H. *pylori* positive and 15 (63%) negative cases (P = 0.74), as well as 11 (31%) H. *pylori* positive and 7 (29%) negative controls (P = 0.91) presented small bowel ulcerative lesions.

Small bowel ulcerative lesions were present in all cases (n = 16) and 1 (5%) control consuming low-dose aspirin only (P < 0.0001); 14 (78%) cases and 2 (9%) controls receiving non-aspirin NSAIDs only (P = 0.0001); 5 cases (83%) and 2 (33%) controls receiving both types of NSAIDs (P = 0.08). 4 (67%) cases receiving cyclooxygenase-2 selective inhibitors and one (16%) control presented small bowel erosions (P = 0.08), while larger lesions presented only in 2 (33%) cases (P = 0.12).

There was no difference between the two groups concerning presence of angiodysplasias [24 (40%) cases *vs* 25 (42%) controls, P = 0.85] and polypoid/submucosal lesions [2 (3%) cases *vs* 2 (3%) controls, P = 1.00].

Clinical course of peptic ulcer hemorrhage

Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with grade-3 or 4 lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). It was 9.9 (SD = 1.5) g/dL in cases with small bowel erosions and 8.6 g/dL (SD = 1.2) in those with larger ulcerative lesions (P = 0.002). Thus calculated hemoglobin drop due to the bleeding episode was 4.7 g/dL in cases with grade 3 or 4 lesions and 3.5 g/dL in cases without ulcerative lesions (P = 0.001).

Cases with small bowel ulcerative lesions necessitated transfusion of 2.8 (SD = 1.2) units of packed red blood cells units while those without 1.1 (SD = 0.6, P < 0.0001). In addition, cases with small bowel ulcers necessitated transfusion of 3.9 (SD = 1.3) packed red blood cells units, while those with small bowel erosions 1.7 (SD = 0.9, P < 0.0001).

After admission and despite successful hemostasis, 7 (32%) cases with small bowel ulcers and none without presented a drop of hemoglobin > 2 g/dL (P = 0.05). Repeat upper gastrointestinal endoscopy revealed peptic ulcer rebleeding in one of them followed by repeat hemostasis, while repeat colonoscopy was negative. In repeat WCE study (because balloon enteroscopy was not available in the country), the remaining patients had at least one small bowel ulcer with a visible vessel on ulcer base with (n = 2) or without active bleeding (n = 4). Five (83%) bleeding recurrences that could possibly attributed to small bowel lesions were mild and self-limited. Nevertheless, one case necessitated operative small bowel endoscopy and hemostasis.

Logistic regression analysis, revealed that presence of diabetes mellitus and chronic obstructive lung disease were independent risk factors for bleeding recurrence possibly attributed to the small bowel, while absence of small bowel ulcers were protective (Table 4).

Thirty-day mortality was zero for both cases and controls and none reported any adverse event related to medical treatment or WCE.

Repeat capsule endoscopy a year later, revealed no ulcerative lesion in patients with small bowel ulcerative lesions in the entry endoscopy, providing that they had stopped NSAIDs during follow-up.

DISCUSSION

In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs presented small bowel erosions and 55% small bowel ulcers. Moreover, 30% of patients with a non-bleeding peptic ulcer consuming NSAIDs had small bowel erosions and 10% small bowel ulcers. Absence of small bowel ulcerative lesions was recorded in patients with peptic ulcer not receiving any NSAIDs. Small bowel ulcerative lesions in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Finally, one out of four small bowel ulcers could bleed during the convalescence period of peptic ulcer bleeding leading to unexplained hemoglobin drop or even melena.

Our study has a number of limitations. It was conducted in a relatively limited number of rather old subjects; the vast majority of whom consumed NSAIDs chronically, while rheumatic disease was excluded. Thus although we included one of the main target groups of NSAID treatment, the elderly, we excluded the other, patients with rheumatic diseases[1]. Our study population old age was a result of reference bias, because our hospital is mainly a Veterans Hospital and referrals from secondary Hospitals usually exclude very young patients. More bowel ulcerative lesions are expected in the elderly because their large[18] and small bowel[19] is more vulnerable to NSAIDs. Patients with rheumatic diseases were excluded because rheumatoid artritis can cause small bowel ulcerative lesions in the absence of NSAID consumption[20]. Rheumatoid arthritis has been related to an increased frequency of iron deficiency anemia[21] and small bowel ulcerative lesions[20], among NSAIDs consumers, but no overt bleeding episodes[21]. Sample size although marginally adequate to explore the role of

aspirin and non-selective NSAIDs, it was insufficient to study the effect of cyclooxygenase-2 selective inhibitors. Proton pump inhibitors were given to all study subjects, a common practice when the study was conducted. Nevertheless recent reports suggest that proton pump inhibitors could exacerbate small bowel ulcerative lesions[22].

Small bowel ulcerative lesions are more frequent in reports including chronic NSAID consumers[1,23] than those including healthy volunteers who received NSAIDs short-term[8,23-26]. A head to head comparison in our study revealed no difference between short and long-term NSAID consumers with concurrent peptic ulcer. Thus, some kind of mucosal adaptation, such as heme oxygenase-1 up regulation[27], could have balanced NSAIDs deleterious effect over time[1].

Small bowel injury and clinically relevant complications associated with the use of NSAIDs, even small dose aspirin, are well recognized[23,25-27]. Nevertheless data on peptic ulcer patients are limited[12]. In our study, prevalence of small bowel ulcerative lesions in NSAID users with non-bleeding peptic ulcer equals the mean of medical literature for non-ulcer NSAIDs consumers[1,23,25-27], even that reported by our group for NSAID consumers with iron deficiency anemia[13]. On the contrary, prevalence of small bowel ulcerative lesions was much higher among NSAID consumers with peptic ulcer bleeding. High prevalence of small bowel mucosal lesions in peptic ulcer bleeders receiving NSAIDs could attributed either to a genetically determined susceptibility for mucosal damage[12] or to an alternated NSAID metabolism due to different CYP2C9 polymorphism[28]. Small bowel ulcerative lesions were 15% more frequent in our study than in Watanabe *et al*[12] report, a small study on 11 non-bleeding gastric ulcer patients receiving low-dose aspirin and proton pump inhibitors. The difference could be attributed to the younger age of Watanabe *et al*[19] patients and the use of low dose aspirin, a less toxic NSAID[11,27]. Inclusion of patients with duodenal ulcer, in our study, could not influence the final outcome, as we found no difference between gastric and duodenal ulcer patients.

Although small bowel mucosal lesions are frequent, small and large bowel complications are infrequent[29], but increase with the exposure to NSAIDs use[9]. Presence of small bowel ulcerative lesions in our non-bleeding ulcer patients was rather indolent, while small bowel ulcers could possibly related to obscure bleeding recurrence in peptic ulcer bleeders. Small bowel ulcers were rather infrequent found in 5%-25% of NSAID consumers[1,23,25-27], but 55% of peptic ulcer bleeders. The probability of small bowel lesions responsible for gastrointestinal bleeding beyond gastric/duodenal ulcers states that we should consider WCE in patients with persistent hemorrhage or bleeding recurrence and negative or inconclusive gastroscopy.

Balloon enteroscopy would have been a preferable option for unexplained bleeding recurrence episodes since it also holds therapeutic capabilities[30]. Nevertheless it was not available in our country during most of the study period.

Gastrointestinal bleeding episodes in NSAID consumers characterized by more severe blood loss and need for more transfusions[31,32], due to co-existence of various co-morbidities and bleeding time prolongation as a result of the antiplatelet effect of NSAIDs[32]. Our study pointed out that small bowel ulcerative lesions could be also important. Old age[33,34], obesity[33,35], presence of diabetes mellitus[35] and chronic obstructive lung disease[33,36] are risk factors for peptic ulcer rebleeding after successful hemostasis because they favor microcirculatory disturbances. Although numbers are too small to draw safe conclusions, our study speculated that presence of diabetes mellitus and chronic obstructive lung disease are important for bleeding recurrence due to small bowel lesions.

In conclusion, more than half patients with peptic ulcer bleeding who consume NSAIDs presented small bowel ulcers. Those lesions were related to lower entry hemoglobin, increased need for blood transfusion and possibly unexplained episodes of bleeding recurrence. Despite study limitations, the results provide a compelling argument for the design of further large-scale studies to define the extent of this potential problem, unravel the mechanisms determining a worse prognosis of patients with peptic ulcer bleeding due to NSAID use and develop strategies to treat small bowel lesions in addition to peptic ulceration.

COMMENTS

Background

Non-steroidal anti-inflammatory drugs are very effectively painkillers, while low-dose aspirin is a common antithrombotic drug. Nevertheless they have been incriminated for causing gastric and duodenal ulcers and their complications, the most common of which is bleeding. Non-steroidal anti-inflammatory drugs can also harm the small bowel. Although small bowel lesions are very common their significance is poorly defined.

Research frontiers

There are very few data pointing out that small bowel ulcers might be very common in patients with gastric ulcers receiving non-steroidal anti-inflammatory drugs. Also it seems that patients receiving non-steroidal anti-inflammatory drugs lose more blood and do worse when they bleed. The explanation given today is that their blood is thinner or that they suffer more co-morbidities, such as heart disease, stroke, lung or kidney diseases.

Innovations and breakthroughs

The authors have found that small bowel ulcers are more common in patients with a gastric or a duodenal ulcer receiving non-steroidal anti-inflammatory drugs and presenting with bleeding than those without bleeding. The authors have also found no small bowel ulcers in patients not receiving non-steroidal anti-inflammatory drugs. The ulcer bug does not affect the possibility to develop small bowel lesions. The authors have shown that small bowel ulcers in patients with bleeding that receive non-steroidal anti-inflammatory drugs mean greater blood loss and need for more transfusions. Final the authors found that in patients with a bleeding from a gastric or a duodenal ulcer that receive non-steroidal anti-inflammatory drugs can relapse not only from their gastric or duodenal ulcer but also from a small bowel ulcer.

Applications

The probability of small bowel lesions responsible for bleeding beyond gastric/duodenal ulcers states that the authors should consider pill camera gut investigation in patients with persistent bleeding or bleeding recurrence and

negative or inconclusive gastroscopy.

Terminology

A gastric or a duodenal ulcer represents a wound in the lining of the stomach or the beginning of the small bowel. The most common causes are the ulcer bug and non-steroidal anti-inflammatory drugs.

Peer review

It is an interesting work.

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P- Reviewer: Almeida N **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Zhang DN

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DOI: 10.4253/wjge.v6.i12.620

World J Gastrointest Endosc 2014 December 16; 6(12): 620-624
ISSN 1948-5190 (online)

CASE REPORT

Novel endoscopic management for pancreatic pseudocyst with fistula to the common bile duct

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Received: July 22, 2014 Revised: September 22, 2014
Accepted: October 14, 2014
Published online: December 16, 2014

Abstract

Pancreatic pseudocyst formation is a well-known complication of pancreatitis. It represents about 75% of the cystic lesions of the pancreas and might be located within or surrounding the pancreatic tissue. Sixty percent of the occurrences resolve spontaneously and only persistent, symptomatic or complicated cysts need to be treated. Complications include infection, hemorrhage, gastric outlet obstruction, splenic infarction and rupture. The formation of fistulas to other viscera is rare and most commonly occurs within the stomach, duodenum or colon. We report a case of a patient with a pancreatic pseudocyst in communication with the common bile duct. There have been only few cases reported in the literature. We successfully managed our case by performing an endoscopic ultrasound-guided drainage of the pancreatic collection and a contemporaneous stenting of the common bile duct. Performed independently, both drainages are effective, safe and well-coded and the expertise on these procedures is widespread. By our knowledge this therapeutic approach was never reported in literature but we retain this is the most correct treatment for this very rare condition.

Key words: Pancreatic pseudocyst; Fistula; Common bile duct; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound

Core tip: In our opinion the combination of endoscopic ultrasound-guided drainage of the pseudocyst and the simultaneous biliary stenting represent the best endoscopic treatment. The advantages of such approach consist in a better evaluation and a more effective drainage of the cystic cavity with the possibility to collect samples for biochemical and bacteriological analysis. Furthermore, the simultaneous biliary stenting can determine, at the same time, a pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

Crinò SF, Scalisi G, Consolo P, Varvara D, Bottari A, Pantè S, Pallio S. Novel endoscopic management for pancreatic pseudocyst with fistula to the common bile duct. *World J Gastrointest Endosc* 2014; 6(12): 620-624 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/620.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.620

INTRODUCTION

Pancreatic fluid collections (PFCs) arise from disruption of a pancreatic duct, with leakage of pancreatic juice

into the surrounding peripancreatic tissues, and comprise about 75% of the cystic lesions of the pancreas[1].

The revised Atlanta classification refers to collections within 4 wk of symptom onset as either acute peripancreatic fluid collections or postnecrotic pancreatic fluid collections depending upon the absence or presence of pancreatic/peripancreatic necrosis, respectively. After 4 wk of the onset of symptoms, persistent collections may gradually develop a fibrous walls and are referred to as pseudocysts (PPs) or walled-off necrosis, again depending upon the absence or presence of necrosis, respectively. In addition, these collections are further classified as sterile or infected[2].

PPs occur as a complication of acute pancreatitis in approximately 10%-20% of cases. Most of these resolve spontaneously[3] and size and duration have not been shown to be the predictors of morbidity and mortality. Expectant management even in asymptomatic large PPs has shown favorable results.

Intervention is only required in patients who develop symptoms[4] such as abdominal pain, mechanical obstruction of the gastric outlet with nausea or vomiting, jaundice for compression of the biliary system, or in whom an infection is suspected for the effective control of sepsis[5].

In recent years, it has gradually been recognized that, due to its lower morbidity rate compared to the surgical and percutaneous approaches, endoscopic treatment may be the preferred first-line approach for managing PFCs[6]. Endoscopic ultrasound (EUS)-guided drainage became the preferred method of draining PFCs which lie within 1 cm of the gastric or duodenal wall, because it presents several advantages: (1) EUS can distinguish PFCs from cystic tumors, the gallbladder and pseudoaneurysm; (2) EUS can determine the content of the PFC, such as if significant necrotic debris is present, which would then require more aggressive endoscopic approach; (3) EUS can identify interposed blood vessels and potentially reduce the risk of bleeding; and (4) EUS permits drainage of non-bulging PFCs[7].

Complications of PPs are uncommon and include sepsis, hemorrhage or pseudoaneurysm formation, rupture with pancreatic ascites, and, rarely, fistula formation to other viscera[8].

The most common sites for fistulas are between PPs and stomach, duodenum, colon and, less commonly, esophagus. Fistulas usually cause pain, inflammation, fever, septicemia, and compression of neighboring structures[9].

Fistulous communication of PPs to the common bile duct (CBD) is uncommon. It affects more frequently males, most common etiology is alcoholic chronic pancreatitis and abdominal pain is the main clinical presentation. To the best of our knowledge, there have been 17 cases reported in the literature[10-23], only three of which managed endoscopically[21-23]. We present a case of this rare condition successfully resolved performing a simultaneous, independent drainage of the PPs and the CBD, never reported in literature.

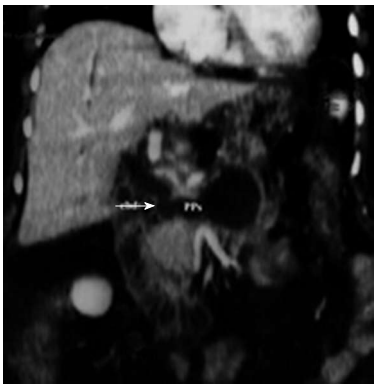

Figure 1 Coronal computed tomography reconstruction showed a large pancreatic pseudocyst with a fistulous communication (arrow) to the common bile duct.

CASE REPORT

Here we describe the case of a 67-year-old Caucasian woman with history of gallstones. She didn't refer alcohol abuse, use of drugs or history of hypertriglyceridemia. She was firstly admitted in our hospital for the onset of acute severe pancreatitis with pancreatic necrosis and acute peripancreatic fluid collection. Ranson score after 48 h was 4. She was managed conservatively and discharged after 4 wk, for the onset of concurrent nosocomial infection (pneumonia). Two weeks later, she developed progressive jaundice, upper quadrants abdominal pain and fever. Laboratory investigation revealed leukocytosis (WBC 20700) and increased indices of cholestasis. Abdominal contrast-enhanced computed tomography (CT) scan (Figure 1) showed in the region of the pancreatic head an 8 cm × 3 cm PPs in communication with the CBD that was dilated (12 mm) such as the intrahepatic bile ducts. Pancreatic duct was normal. Subsequently, the patient underwent endoscopic retrograde cholangiopancreatography (ERCP) that revealed a long, distal biliary extrinsic compression and confirmed a fistulous communication between middle tract of the CBD and large PPs in the head of the pancreas. Biliary sphincterotomy was performed and a 10 Fr × 7 cm plastic stent was placed in the CBD.

The duodenoscope was switched for an echoendoscope: at EUS the PPs resulted relatively thin-walled, with optimal contact with the gastric wall, within abundant echoic debris and encompassing both splenic vessels. Doppler assessment excluded large vessels interposition and EUS-guided drainage was performed. A 19-gauge dedicated needle (ECHO-HD-19-A, Wilson-Cook Medical Inc., Winston-Salem, North Carolina, United States) was used for the puncture of the collection (Figure 2A) and brown-purulent fluid was aspirated for bacteriological examination. A first 0.035-inch guidewire (Jagwire; Microvasive Endoscopy, Boston Scientific Corp., Natick, Massachusetts, United States) was advanced

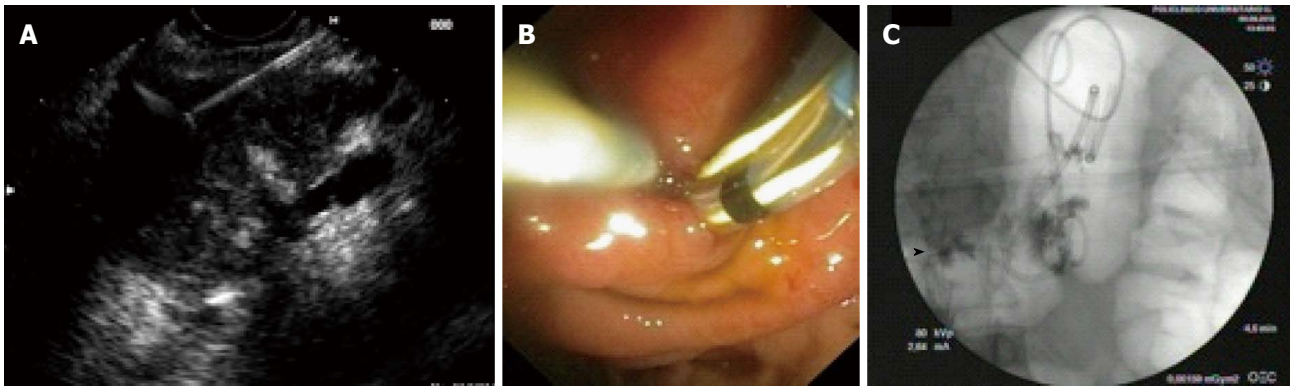

Figure 2 Pancreatic pseudocystis intervention. First step: Endoscopic ultrasound-guided puncture with 19-gauge dedicated needle of the pancreatic collection containing necrotic debris (A); Second step: Placement of the first plastic stent and two guidewire into the pseudocysts (PPs) for the placement of the second stent and the nasocystic drain (B); Third step: Fluoroscopic image showing the biliary stent (arrowhead), two PPs double pigtail stents and the nasocystic drain (C).

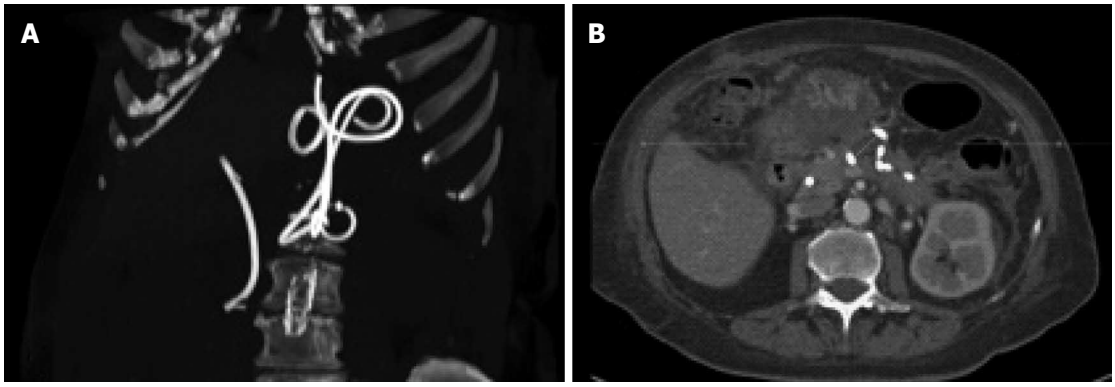

Figure 3 Computed tomography scan performed three weeks later: Scan reconstruction showing the correct position of the biliary and pancreatic collection stents (A), while the axial scan show almost complete resolution of the cystic cavity (B).

into the PPs through the inner part of the needle under fluoroscopic guidance and dilation of the fistula was obtained using a 8 mm biliary dilation balloon over the guidewire. After placing a first 10 Fr × 6 cm double pigtail plastic stent, two more 0.035-inch guidewires were placed into the collection through a catheter (Figure 2B) and a second 10 Fr double pigtail stent and a 7 Fr nasocystic catheter were then inserted (Figure 2C).

Bacterial culture from the pancreatic fluid collection resulted positive for Klebsiella Pneumonie. The patient was started on antibiotics and daily collection aspiration and washing was performed trough the nasocystic drainage. After 5 d the patient was in good clinical condition and was discharged and scheduled for the follow up. Three weeks later CT scan showed the correct position of the biliary and cystic stents (Figure 3A) and revealed a quite complete reduction of the cystic cavity (Figure 3B); the nasocystic drain was than removed.

Three months later, ERCP was performed for removing the biliary stent: cholangiography revealed, after high-pressure contrast injection with a balloon catheter, the resolution of the biliary fistula (Figure 4). Both double pigtail plastic stents were leaved in place in the stomach and removed only after a further 6 mo follow up. Patient was followed for 8 mo without evidence of recurrence of the pseudocyst.

DISCUSSION

Fistulous communication of PFCs to the CBD is distinctly rare. Clinical symptoms, as in our case, are generally right upper quadrant abdominal pain, jaundice and fever.

Management of this rare condition is not defined and, in literature, only seventeen cases have been reported, ten of whom were treated surgically, three with percutaneous external drainage and one was observed. Only three cases were endoscopically managed. Carreere *et al*[21] treated one patient with biliopancreatic fistula with transpapillary pancreatic stenting for 5 mo.

Boulanger *et al*[22] reported a case of PPs with fistula to the common bile duct demonstrated at ERCP and endoscopically managed with biliary stent and, simultaneously, with a second stent placed *via* a transpapillary route across the fistula with one end into the pseudocyst and the other end into the duodenum. Authors don't mention for how long both stents were leaved in place. Al Ali *et al*[23] performed the same endoscopic procedure. In this case, a double pigtail stent placed *via* the transpapillary route across the fistula into

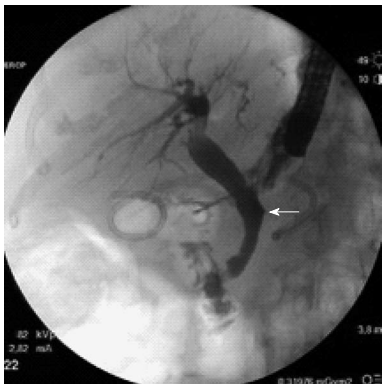

Figure 4 At endoscopic retrograde cholangiopancreatography performed 3 mo later, complete healing of the fistula was documented (arrow).

the PPs was leaved in place for 2 mo.

In our case, we successfully endoscopically managed large PPs with a fistulous communication to the CBD and within necrotic debris, by positioning a plastic biliary stent in association with simultaneous EUS-guided transgastric pancreatic collection drainage with two double pigtail stents and a nasocystic drain.

We believe that this endoscopic approach, especially in cases of very large and infected collection with necrotic debris, should be preferred to the previously described in literature for the better evaluation and the more effective drainage of the cystic cavity. Another advantage of this combined approach is that EUS provides a detailed view of the pseudocyst, the surrounding vascular structures, the anatomy of the region and can determine the content of the PFCs, such as whether it is a simple collection or if significant necrotic debris is present, which would then require a more aggressive endoscopic approach[24]. During the EUS-guided procedure is also possible to aspirate the collection content for biochemical and bacteriological analysis. For these and other reasons, EUS-guided drainage has become the standard procedure for treating symptomatic pancreatic fluid collections[25] and the expertise on this technique is widespread. The simultaneous biliary and pancreatic collection drainage determine, at the same time, a pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

In conclusion, this is the first case reported in literature of this rare condition treated with two simultaneous endoscopic procedures, both well coded and safe for the patient, resulted in a rapid healing.

COMMENTS

Case characteristics

A 67-year-old Caucasian woman with history of gallstones and severe acute pancreatitis was admitted to hospital for jaundice, fever and abdominal pain two wk after pancreatitis resolution.

Differential diagnosis

Cholangitis, pancreatitis.

Laboratory tests

WBC 20700 and increased indices of cholestasis.

Imaging diagnosis

Computed tomography scan showed in the region of the pancreatic head an 8 cm x 3 cm pancreatic pseudocyst in communication with the common bile duct (CBD) that was dilated (12 mm) such as the intrahepatic bile ducts; endoscopic retrograde cholangiopancreatography (ERCP) revealed a long, distal biliary extrinsic compression and confirmed a fistulous communication of the middle tract of the CBD with a large pancreatic pseudocyst in the head of the pancreas.

Treatment

Biliary sphincterotomy was performed and a 10 Fr x 7 cm plastic stent was placed in the common bile duct to allow the closure of the fistula. The pseudocyst was drained by endoscopic ultrasound (EUS) and two double pigtail stents were placed between the wall of the stomach and that of pseudocysts for complete drainage.

Experiences and lessons

This case describes a new endoscopic treatment obtained by combination of EUS-guided drainage of the pseudocyst and simultaneous biliary stenting. The advantages of such approach consist in a better evaluation and a more effective drainage of the cystic cavity with the possibility to collect samples for biochemical and bacteriological analysis. Furthermore biliary stenting determines pressure reduction in the bile system and in the pancreatic collection facilitating the healing of the fistula.

Peer review

The authors reported a case of pancreatic pseudocyst with fistula connection with the bile duct that was successfully treated with ERCP stenting and EUS drainage.

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P- Reviewer: Hu R, Teoh AYB, Voutsas V **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Zhang DN

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v6.i12.625

World J Gastrointest Endosc 2014 December 16; 6(12): 625-629
ISSN 1948-5190 (online)

CASE REPORT

Life threatening bleeding from duodenal ulcer after Roux-en-Y gastric bypass: Case report and review of the literature

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Received: May 28, 2014 Revised: October 15, 2014
Accepted: October 28, 2014
Published online: December 16, 2014

Abstract

Acute upper gastrointestinal bleeding is a rare, but serious complication of gastric bypass surgery. The inaccessibility of the excluded stomach restrains postoperative examination and treatment of the gastric remnant and duodenum, and represents a major challenge, especially in the emergency setting. A 59-year-old patient with previous history of peptic ulcer disease had an upper gastrointestinal bleeding from a duodenal ulcer two years after having a gastric bypass procedure for morbid obesity. After negative upper endoscopy finding, he was urgently evaluated for gastrointestinal bleeding. At emergency laparotomy, the bleeding duodenal ulcer was identified by intraoperative endoscopy through gastrotomy. The patient recovered well after surgical hemostasis, excision of the duodenal ulcer and completion of the remnant gastrectomy. Every general practitioner, gastroenterologist and general surgeon should be aware of growing incidence of bariatric operations and coherently possible complications after such procedures, which modify patient's anatomy and physiology.

Key words: Roux-en-Y gastric bypass; Duodenal ulcer; Bleeding; Endoscopy; Emergency surgery

Core tip: Bleeding duodenal ulcer after Roux-en-Y gastric bypass for morbid obesity is a rare, but life threatening situation. Anatomic rearrangement after bariatric operation prevents upper endoscopy from displaying stomach remnant, duodenum, and proximal jejunum. The bleeding duodenal ulcer was identified at emergency laparotomy by intraoperative endoscopy through gastrotomy. After surgical hemostasis, duodenal ulcer excision and completion of the remnant gastrectomy the postoperative course was uneventful.

Ivanecz A, Sremec M, Ćeranić D, Potrč S, Skok P. Life threatening bleeding from duodenal ulcer after Roux-en-Y gastric bypass: Case report and review of the literature. *World J Gastrointest Endosc* 2014; 6(12): 625-629 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/625.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.625

INTRODUCTION

Obesity in general is described as a global epidemic problem with growing prevalence by World Health Organization[1]. Bariatric surgery has been identified as a safe and effective treatment possibility for morbid obesity and allied comorbidities[2]. Increasing number of bariatric procedures correspond with severity of postsurgical complications[3].

Roux-en-Y gastric bypass (RYGB) is a frequent

surgical procedure for these patients[2]. A significant flaw of RYGB is interrupted access to the bypassed stomach remnant by conventional endoscopy or contrast radiography[4,5]. Interrupted access could be a problem for evaluation and treatment of pathology in the bypassed gastric remnant. Severe complications in area of gastric remnant have been already reported, although the incidence of these complications following RYGB is very low[5-7]. There are retrospective series with 3000 cases of open RYGB presented, 8 patients (0.3%) had bleeding from peptic ulcer disease in the bypassed remnant and intestine[8,9]. Hemorrhage after RYGB could be early or late and in the literature is mostly limited to case reports only[10-12]. Although upper gastrointestinal bleeding originating from ulceration is infrequently reported, it could be a fatal complication.

This report describes the case of a 59-year-old patient, presented in an emergency setting with a life threatening bleeding from duodenal ulcer two years after RYGB.

CASE REPORT

A 59-year-old man presented to the emergency department complaining of weakness, faint and melena. His symptoms started one week before, with passing of darker stool. On the day he was admitted, he visited the market-place, where he fainted. On admission, the patient was pale, normotensive (126/76 mmHg), normocardic (89 per minute) and normopneic (16 per minute) with 85% SpO2. Anal exam showed melena.

His medical history included peptic ulcer disease, psoriatic arthritis and laparoscopic cholecistectomy. The patient has been overweight (BMI 50 kg/m^2) in the past and underwent successful bariatric procedure two years prior at another institution. At the time of admission, there have been no data on exact type of bariatric surgery performed. The patient was a nonsmoker and denied alcohol abuse. The patient was on nonsteroidal anti-inflammatory medication (NSAID). Every day medications included diclofenac (100 mg) two times a day and combination of tramadol with paracetamol (37.5/325 mg) two times a day and once a week 12 mg of metotrexat. At the time of emergency admission, the patient had no prescription for any antiulcer drugs.

Laboratory results revealed decreased level of hemoglobin (83 g/L) and hematocrit (0.24) and coagulopathy. Despite multiple blood transfusions - 4 units of packed red blood cells administered - the patient's anemia persisted. Two hours after admission an emergency upper endoscopy exposed a typical gastrojejunal anastomosis and was advanced 30 cm beyond, without evidence of active bleeding or clot. A longer pediatric endoscope was introduced. During endoscopy patient fainted again and felt stronger abdominal pain. The patient continued to maintain normal blood pressure and pulse. He was transferred to intensive care unit (ICU). A computed tomography (CT) scan demonstrated marked distention of a fluid-filled gastric remnant, a wider duodenal wall, and multiple fluid levels through proximal small intestine (Figure 1). No source of active bleeding was revealed.

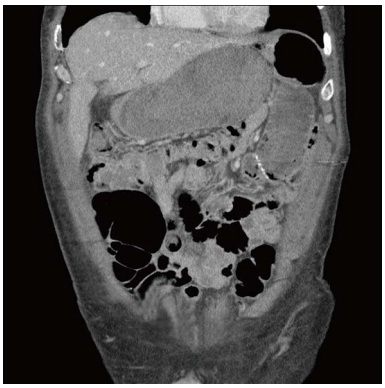

Figure 1 Computed tomography scan showed a fluid-filled gastric remnant, a wider duodenal wall, and multiple fluid levels through proximal small intestine.

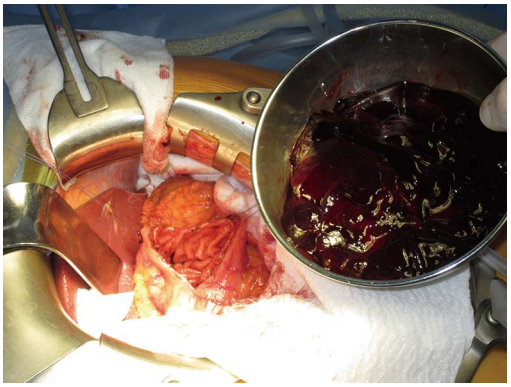

Figure 2 Blood evacuated from gastric remnant.

As a result of ongoing hemorrhage, six hours after admission the patient was taken immediately to the operating room. An emergency midline laparotomy was undertaken.

At surgical exploration a distended gastric remnant, filled with blood was revealed (Figure 2). The duodenum and the proximal jejunal loops were also filled with blood. Through gastrotomy the clothed blood was evacuated and the gastric remnant explored. No active bleeding was identified. Gastrotomy was extended distally to the pyloric region. There were no signs of bleeding; only bile was seen at this part. The duodenal region was covered by visceral adhesions after previous cholecistectomy; no external signs of ulceration could be identified. An intraoperative endoscopy performed trough gastrotomy showed a large ulcer in the posterior part of the second portion of the duodenum with a bleeding branch of gastro-duodenal artery at the bottom (Figure 3). Endoscopic hemostasis with adrenaline injection was ineffective. A gastrotomy was extended once again to duodenotomy and the bleeding ulcer was over-sewn with stitches. Additionally the gastroduodenal artery

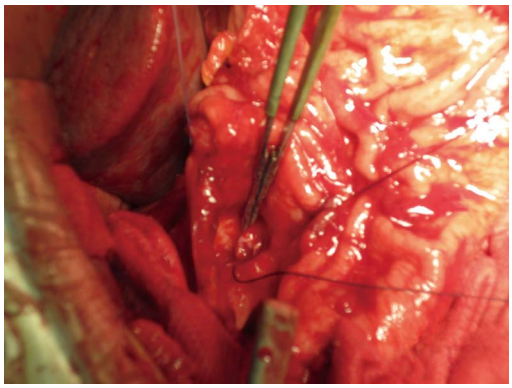

Figure 3 Thirty millimeters wide ulcer on the posterior part of the second portion of the duodenum with a bleeding branch of gastro-duodenal artery marked with tweezers.

was ligated. The ulcer was excised together with first part of the duodenum and the stomach was mobilized to complete the remnant gastrectomy. The duodenal stump was closed primarily in two layered suture line with second layer fixing the stump to the head of the pancreas.

The first postoperative day was characterized by secretion of 1500 mL sero-hemorrhagic fluid trough drains. After initial improvement, decreasing hemoglobin levels were detected again. A relaparotomy was indicated, which revealed a 1 L of clothed blood in the upper abdominal cavity. No source of active bleeding was identified. The blood was evacuated, and the laparotomy closed.

The further postoperative course was uneventful and on 11th post-operative day the patient was discharged. After three months the patient was in very good shape with normal values of hemoglobin.

Histopathology revealed no *Helicobacter pylori* infection in duodenal or gastric tissue. Ulcer was 30 millimeters wide without any neoplastic or dysplastic cells.

DISCUSSION

Acute bleeding duodenal ulcer after Roux-en-Y gastric bypass for morbid obesity is a rare, but life threatening situation[10-12]. The presented patient developed first episode of such complication two years after bariatric operation at another institution. The type of previous surgical procedure (RYGB) was identified only after upper endoscopy and CT scan. The etiology of bleeding was unclear and continued despite aggressive volume replacement and multiple blood transfusions. Urgent laparotomy was the safest option in this life threatening situation. The patient had undergone intraoperative gastrotomy and intraoperative endoscopy through the gastrostomy. An active bleeding from duodenal ulcer was found and managed surgically. Additionally a remnant gastrectomy was performed.

There are many important issues, which should be emphasized in this case. Firstly, bariatric operations are frequently performed in Europe and United States[2]. With increasing number of such procedures, physicians should be familiar with its possible complications. In the emergency setting, the possible pitfall is not to known which type of bariatric surgery patient have had in the past. As in the reported case, the anatomical landmarks of RYGB were revealed only after endoscopic and CT investigations, while in the meantime dealing with threatening hemorrhagic shock.

Another point of interest is the rarity of this late complication. Bleeding from marginal ulcers localized near the pouch-enteric anastomosis is not uncommon after RYGB and could be easily diagnosed and managed by conventional endoscopy[2,13-16]. Bleeding duodenal ulcer after RYGB is rarely reported and it is mostly limited to case reports only[3,13,17-19].

Another issue of this report is difficulty of the diagnostic workup. Evaluation of the bypassed gastric remanant in patients with the possibility of bleeding peptic ulcer disease could be a major challenge. Endoscopic access becomes very difficult after RYGB because of excluded part of the stomach, duodenum, proximal jejunum, and biliary tree[9,20]. Conventional endoscopy of the gastric remnant and duodenum is not possible any more[2]. The long 90-150 cm Roux limb disables endoscopic approach, even with specialized instruments[3,9]. Many different methods have been suggested for displaying the bypassed gastrointestinal tract. These include endoscopy *via* percutaneous gastrostomy access, retrograde endoscopy and virtual gastroscopy using CT scan[21]. In our experience, it has been impossible to visualize the duodenum - even with longer pediatric endoscopes. A minimally invasive technique to access the bypassed stomach after RYGB for endoscopic diagnosis and treatment is described in the literature[9]. Ceppa *et al*[9] proposed a laparoscopic transgastric endoscopy. Such an approach was unattractive in this patient, where highly emergent ongoing bleeding from duodenal ulcer was present.

A special point of interest of this case concerns the proton-pump inhibitors regimens after RYGB. There are non-clear directives for managing patients after RYGB in this regard; however some surgeons advise lifelong proton-pump inhibitors for all patients undergoing RYGB surgery[22]. This patient underwent a complete diagnostic workup before bariatric surgery including upper endoscopy, and duodenal ulcer was diagnosed appropriately. Moreover, the patient was on every day therapy with NSAID for psoriatic arthritis. After the successful RYGB surgery, proton-pump inhibitors were prescribed for several months. Later, proton-pump inhibitors were abandoned. The reason for this is unclear.

Finally, the variety of the surgical management represents another point of interest. When the general and/or the hemodynamic status of the patient are critical, the surgical management should be limited only to a hemorrhage control[16]. After prompt control of the hemorrhage the surgical management was extended

to resection of the gastric remnant. The rationale for this decision was to prevent the development of further possible complications, which include re-bleeding, perforation and gastric malignancy.

In conclusion, due to growing incidence of bariatric operations and possible complications, all healthcare professionals involved in the diagnostic workup of these patients, should be familiar with such procedures which modify patient's anatomy and physiology. They should also be aware of the limitations of imaging methods, including urgent endoscopy.

ACKNOWLEDGMENTS

Written informed consent for this case report was derived from the patient for the purpose of publication. A copy of the document could be presented for review by the Editor-in-Chief of this journal.

COMMENTS

Case characteristics

An 59-year-old male after gastric bypass procedure for morbid obesity with gastrointestinal bleeding.

Clinical diagnosis

The patient presented to the emergency department complaining of weakness, fainting, and melena.

Differential diagnosis

Unexplained hemorrhagic shock with severe abdominal pain.

Laboratory diagnosis

WBC 11.40 k/uL; HGB 8.30 gm/dL; coagulopathy with decreased levels of prothrombine; other liver function test were within normal limits.

Imaging diagnosis

CT scan showed marked distention of a fluid-filled gastric remnant and multiple fluid levels through proximal small intestine. Intraoperative endoscopy confirmed bleeding duodenal ulcer.

Pathological diagnosis

The excised duodenal ulcer was 30 millimeters wide and without any neoplastic or dysplastic cells.

Treatment

At emergency laparotomy, the bleeding duodenal ulcer was identified by intraoperative endoscopy through gastrotomy. Surgical hemostasis, excision of the duodenal ulcer and completion of the remnant gastrectomy was performed.

Related reports

Bariatric surgery modify patient's anatomy and physiology. The treating physicians should be aware of the limitations of imaging methods, including urgent endoscopy.

Term explanation

Roux-en-Y gastric bypass is a common surgical procedure for morbid obese patients.

Experiences and lessons

The increasing number of bariatric procedures correspond with the severity of postsurgical complications.

Peer review

Nice case presentation: succint, linguistically correct, the references are well chosen and conform requirements of the Journal.

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P- Reviewer: Buzas GM, Kate V **S- Editor**: Ji FF **L- Editor**: A
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DOI: 10.4253/wjge.v6.i12.630

World J Gastrointest Endosc 2014 December 16; 6(12): 630-634
ISSN 1948-5190 (online)

CASE REPORT

Endoscopic therapy for esophageal hematoma with blue rubber bleb nevus syndrome

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Author contributions: Sato M and Watanabe K managed the patients; Takagi T and Watanabe K performed the endoscopic examination; Suzuki R, Nakamura J, Sugimoto M, Waragai Y, Kikuchi H and Konno N provided clinical advice; Takasumi M and Hikichi T collected the data and wrote the paper; Hikichi T revised the paper; Obara K, Watanabe H and Ohira H supervised the report; all authors approved the final manuscript for publication.

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Received: August 9, 2014 Revised: October 8, 2014
Accepted: October 28, 2014
Published online: December 16, 2014

Abstract

A 57-year-old woman previously diagnosed with blue rubber bleb nevus syndrome (BRBNS) reported hematemesis. BRBNS is a rare vascular anomaly syndrome consisting of multifocal hemangiomas of the skin and gastrointestinal (GI) tract but her GI tract had never been examined. An upper gastrointestinal endoscopy revealed a large bleeding esophageal hematoma positioned between the thoracic esophagus and the gastric cardia. An endoscopic injection of polidocanol was used to stop the hematoma from bleeding. The hematoma was incised using the injection needle to reduce the pressure within it. Finally, argon plasma coagulation (APC) was applied to the edge of the incision. The esophageal hematoma disappeared seven days later. Two months after the endoscopic therapy, the esophageal ulcer healed and the hemangioma did not relapse. This rare case of a large esophageal hematoma originating from a hemangioma with BRBNS was treated using a combination of endoscopic therapy with polidocanol injection, incision, and APC.

Key words: Blue rubber bleb nevus syndrome; Endoscopic injection sclerotherapy; Incision; Esophageal hematoma; Esophageal hemangioma

Core tip: A patient with a large hemorrhagic esophageal hematoma complicated with blue rubber bleb nevus syndrome was treated using endoscopic injection with polidocanol and incision with an injection needle. The hematoma was then treated with argon plasma coagulation.

Takasumi M, Hikichi T, Takagi T, Sato M, Suzuki R, Watanabe K, Nakamura J, Sugimoto M, Waragai Y, Kikuchi H, Konno N, Watanabe H, Obara K, Ohira H. Endoscopic therapy for esophageal hematoma with blue rubber bleb nevus syndrome. *World J Gastrointest Endosc* 2014; 6(12): 630-634 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i12/630.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i12.630

INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular anomaly syndrome consisting of multifocal

hemangiomas of the skin and gastrointestinal (GI) tract. GI bleeding is a frequent complication that often presents with anemia as a result of chronic occult blood loss. Mortality depends on the GI involvement because it is difficult to treat GI bleeding. The use of endoscopic treatment of GI bleeding for hemangiomas has been reported[1,2]. We treated a single case of a large esophageal hematoma caused by a hemangioma. The treatment involved endoscopic injection, incision of the hematoma using an injection needle, and argon plasma coagulation (APC).

CASE REPORT

A 57-year-old woman was diagnosed with BRBNS because of skin hemangiomas since teen. However, her GI tract had never been examined. The patient had no anemia that suggested occult GI bleeding. She had no other history and did not take any drugs, including anti-thrombotics. In July 2011, she was admitted to a previously attended hospital complaining of hematemesis. An upper GI endoscopy showed a bleeding esophageal hematoma from the thoracic esophagus to the gastric cardia. We treated with total parenteral nutrition and nothing by mouth before endoscopic treatment, however, her anemia progressed. She was referred to our hospital because her hematoma had suspected esophageal or gastric varices.

A physical examination at admission revealed a scar on her left breast from hemangioma resection and multiple bluish hemangiomas on her left arm (Figure 1). She had a height of 154 cm and a weight of 60 kg. The patient's vital signs were stable: blood pressure 120/72 mmHg, heart rate 92 beats per minute, body temperature 36.3 ℃, and SpO2 100% (room air). Laboratory data showed anemia, with a hemoglobin level of 7.4 g/dL. However, a mean corpuscular volume 95.6 fl suggested no chronic bleeding. The patient's white blood cell count, liver function, renal function, and electrolyte balance were normal. The blood urea nitrogen/creatinine ratio was normal. The D dimer level was high (101.7 μg/mL) because of hypercoagulation in multiple hemangiomas. Dynamic computed tomography (CT) revealed an esophageal hematoma but no marked hemoperfusion to the hematoma (Figure 2). Upper GI endoscopy showed a growing esophageal hematoma with oozing bleeding (Figure 3A and B). The hematoma was large and bulging, and it was difficult to pass the endoscope over the hematoma. We inferred that this hematoma originated from hemangiomas related to BRBNS and that the hematoma had slow inflow from vessels such as esophageal varices because it had grown since it was identified at the other hospital. The patient had no history of vomiting, abdominal straining after excessive eating and drinking.

We first used endoscopic injection with polidocanol (aethoxysclerol; ASKA Pharmaceutical Co. Ltd.) as a sclerosant for endoscopic injection sclerotherapy (EIS) for esophageal varices. This agent was used to obstruct the inflow vessels to the hematoma because it was dependent on esophageal varices. Twenty-four ml of 1% polidocanol was injected into the hematoma using a 23 G injection needle (Varixer; TOP Corp., Tokyo, Japan) (Figure 3C). Ten minutes after polidocanol injection, the hematoma was incised using the same injection needle to reduce the pressure within it (Figure 3D). Finally, argon plasma coagulation (APC: APC300; Amco Corp., Tokyo, Japan) was applied to the edge of the incision. We finished the endoscopic procedure because no active bleeding or oozing from the hematoma occurred. The

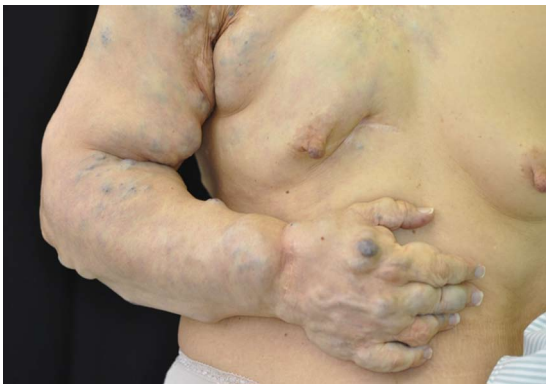

Figure 1 Physical examination at admission. The patient had a scar from the excision of hemangiomas on her right breast and multiple bluish hemangiomas on her right arm.

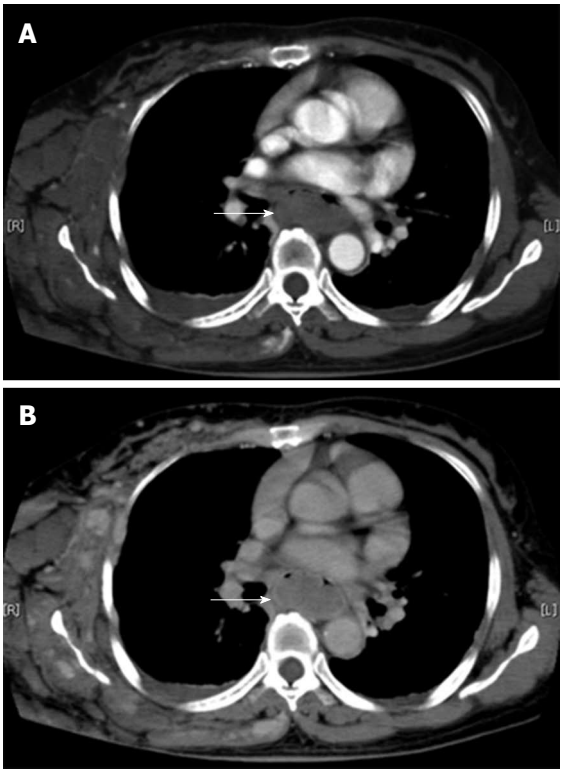

Figure 2 Dynamic computed tomography study. A: Early phase; B: Late phase. An esophageal hematoma was found, but there was no hemoperfusion to the hematoma.

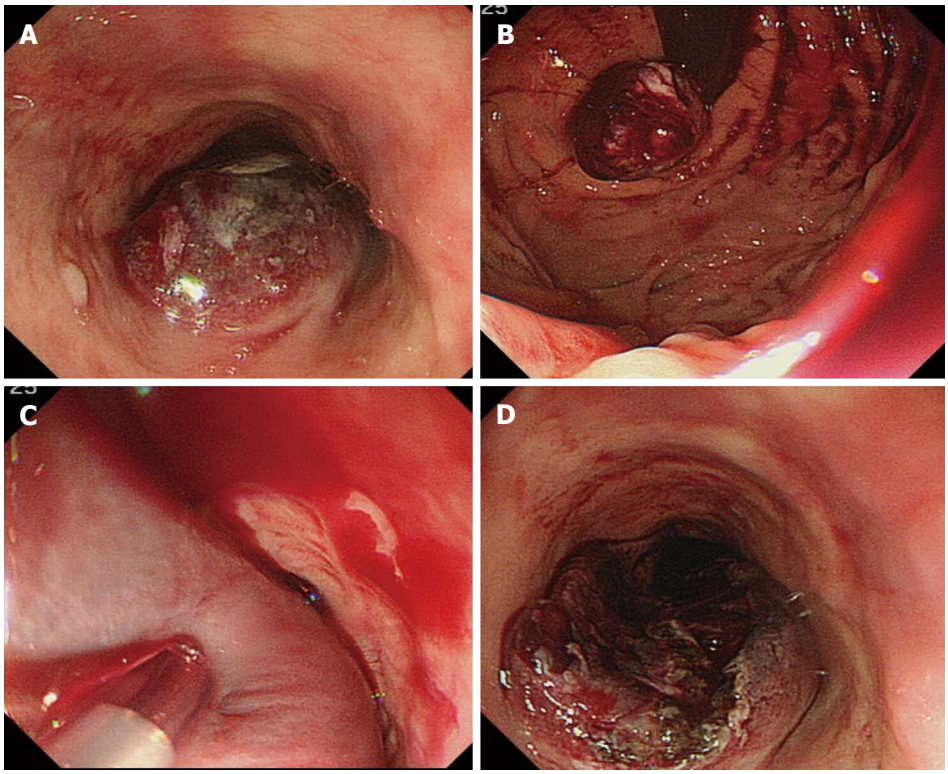

Figure 3 Endoscopic images of the esophageal hematoma taken before and during endoscopic therapy. A and B: Esophageal hematoma from the thoracic esophagus to the gastric cardia with oozing bleeding; C: Endoscopic injection sclerotherapy with polidocanol was applied to the hematoma; D: After injection of polidocanol, the hematoma was incised using an injection needle.

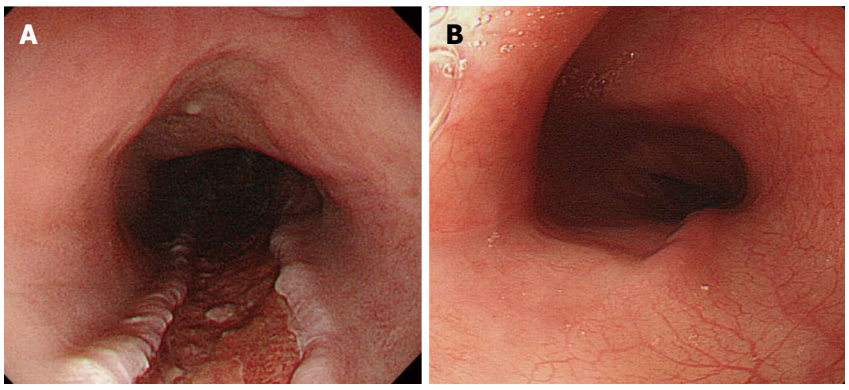

Figure 4 Endoscopic images after endoscopic therapy. A: Seven days after endoscopic therapy, the hematoma had disappeared; B: Two months after endoscopic therapy, the esophageal ulcer healed, and the hematoma had not relapsed.

patient received six units of transfused blood. Seven days after the treatment, upper GI endoscopy showed that the hematoma had disappeared (Figure 4A). The anemia did not progress. A liquid diet was started and was increased gradually to solid food. Ten days after endoscopic therapy, colonoscopy (CS) and capsule endoscopy (CE) were performed to check other hemorrhagic lesions and hemangiomas related to BRBNS in the small intestine and colon. Although CS revealed no hemangiomas, CE revealed a bluish lesion that implied the existence of a hemangioma in the small intestine. Two months after the endoscopic therapy, the esophageal ulcer healed and the hemangioma did not relapse (Figure 4B).

DISCUSSION

BRBNS is a rare disease associated with multiple rubbery cavernous hemangiomas on the skin and GI tract mucosa. Bean[3] first described BRBNS with cutaneous and GI malformations in 1958. The incidence of this syndrome is very low, and only approximately 200 cases have been described in the literature[4]. Histologically, BRBNS hemangiomas correspond to venous malformations. Vascular malformations are similar to hemangiomas and consist of abnormal vascular channels lined with a single layer of dysplastic endothelium. However, these lesions do not regress the way hemangiomas do. Vascular

malformations are present at birth and are congenital[5]. They consist of mature endothelial-lined channels with insufficient surrounding smooth muscle[6]. For convenience, we use the words "hemangioma" to describe both vascular malformations and hemangiomas in this case report. Hemangiomas related to BRBNS have no malignant potential. However, the most important clinical concern is the high probability of fatal GI bleeding or chronic severe anemia[1]. The GI involvement in BRBNS is typically minimal, circumscribed, and multifocal[6]. The most common site of bowel involvement in BRBNS is the small intestine. In the case described in this study, CE revealed suspected hemangiomas. An upper GI endoscopy revealed a large intramural hematoma, but no hemangioma. The exact pathogenesis of the intramural hematoma in the esophagus is unclear. Intramural esophageal hematomas are generally characterized by a hemorrhagic episode that starts within the submucosa of the esophagus. Vomiting and abdominal straining, prior endoscopic procedures, and bleeding disorders are the common predisposing factors[7]. We were unable to prove that the hematoma had originated from a hemangioma due to BRBNS because the patient's GI tract was not examined. However, we inferred that the large hematoma was related to the hemangiomas related to BRBNS because no other trigger such as vomiting or excessive eating or drinking was found.

EIS has been widely used to treat esophageal varices. We first considered that the pathology of the large hematoma was similar to esophageal varices. Intramural hematoma of the esophagus is reportedly a rare complication after EIS[8,9]. An intramural hematoma after EIS is an iatrogenic complication. It is formed by blood inflow because of faulty EIS. The use of an incision to treat the intramural hematoma after EIS was needed to reduce the pressure of the large hematoma and prevent its growth[9]. Although CT did not reveal inflow vessels to the hematoma in this case, we inferred that the hematoma was enlarged by slight and slow inflow from esophageal vessels. We selected endoscopic injection using polidocanol before incision to obstruct the inflow vessels to the hematoma and prevent the risk of bleeding. The hematoma was then incised using the same injection needle after confirmation that there was no bleeding from the pinhole or hematoma growth. Finally, APC was applied to the edge of the incision to stop any oozing bleeding that occurred after the incision. The presence of oozing bleeding after the incision suggested there was slow inflow to the hematoma. Seven days after endoscopic treatment of the hematoma, upper GI endoscopy showed that it had disappeared. The combination treatment consisting of endoscopic therapy, polidocanol injection, incision, and APC was effective.

An intramural hematoma of the esophagus might resolve spontaneously without therapeutic intervention and have a benign course[8]. However, the hematoma in this patient expanded and was growing. Symptom relief was rapid after incision of the hematoma. The patient was able to resume eating sooner than might have been predicted based on prior reports[7-11]. Following conservative therapy, symptoms usually begin to resolve 36-72 h after treatment and disappear completely in 2-3 wk[8]. The start of oral intake was sooner than previous cases[9-11]. It was possible for our patient to resume oral intake three days after the endoscopic incision, although it took approximately one week with conservative therapy in other studies[7,8]. In conclusion, a large esophageal hematoma from a bleeding hemangioma with BRBNS was treated using endoscopic techniques. It is noteworthy that an incision of the hematoma prevented its growth. This method is regarded as applicable not only to hematoma with BRBNS but also to hematomas with other GI diseases.

COMMENTS

Case characteristics

A 57-year-old woman previously diagnosed with blue rubber bleb nevus syndrome (BRBNS) reported hematemesis.

Clinical diagnosis

An upper gastrointestinal endoscopy showed a bleeding esophageal hematoma from the thoracic esophagus to the gastric cardia.

Differential diagnosis

Esophageal varices and intramural hematoma of the esophagus.

Laboratory diagnosis

Laboratory data showed anemia with a hemoglobin level of 7.4 g/dL; however, mean corpuscular volume 95.6 fL suggested no chronic bleeding.

Imaging diagnosis

Dynamic computed tomography revealed an esophageal hematoma but no marked hemoperfusion to the hematoma.

Pathological diagnosis

No histological examination was done in this case.

Treatment

Endoscopic treatment of polidocanol injection was applied, with incision by injection needle and argon plasma coagulation to the hematoma.

Related reports

The incidence of BRBNS is very low. Approximately 200 cases have been described in the literature. Moreover, very few cases of intramural hematoma of the esophagus treated with endoscopy have been reported in the literature. Their treatment is controversial.

Term explanation

It is noteworthy that an incision of the hematoma prevented its growth. This method is regarded as applicable not only to hematoma with BRBNS but also to hematomas with other GI diseases.

Experiences and lessons

This case demonstrates that treatment of esophageal intramural hematoma using endoscopic techniques was more effective than conservative therapy to relieve her symptoms rapidly.

Peer review

The authors have described a case of esophageal hematoma with BRBNS that was treated using endoscopic techniques. The article describes novel treatment applied to an intramural hematoma of the esophagus.

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ISSN 1948-5190 (online)

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World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Launch date

October 15, 2009

Frequency

Monthly

Editorial office
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Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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