Techniques in Gastrointestinal Endoscopy 17 (2015) 12–18

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Obscure gastrointestinal bleeding and iron-deficiency anemia—Where does capsule endoscopy fit?

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ARTICLE INFO

Article history:
Received 15 December 2014
Accepted 22 February 2015

Keywords:
Capsule endoscopy
Obscure GI tract bleeding
Iron-deficiency anemia
Device-assisted enteroscopy
CT enterography

ABSTRACT

The evaluation of patients with obscure gastrointestinal bleeding (OGIB) and iron-deficiency anemia (IDA) has been suboptimal for a long time, mainly owing to the limitations of techniques for the study of the small bowel. Since the introduction of capsule endoscopy (CE) and device-assisted enteroscopy (DAE), the diagnostic and therapeutic approaches to OGIB have improved significantly. CE allows the evaluation of the entire small bowel mucosa, providing high-quality images and identifying mucosal changes (ie, vascular malformations, inflammatory changes, mass, or polyps), whereas DAE ensures an effective therapeutic approach. Many studies have shown that the diagnostic yield (DY) of CE in patients with OGIB and IDA (~50%) is similar to that of DAE and significantly superior to the DY of other imaging modalities for the small bowel. Nowadays, CE is considered the examination of choice in patients with OGIB or IDA, after negative gastroscopy and ileocolonoscopy results. The DY of CE is increased in patients with overt bleeding, or when the procedure is performed closely to an acute episode of bleeding, as well as in patients with severe IDA or high transfusion requirement. CE is also an effective tool in directing further diagnostic or therapeutic interventions (ie, deciding the optimal insertion route of DAE). Moreover, numerous studies have also shown that CE-based strategies affect the management of patients with OGIB.

1. Introduction

Obscure gastrointestinal tract bleeding (OGIB) is defined as gastrointestinal (GI) tract bleeding of unknown origin that persists or recurs, following a negative initial endoscopic evaluation (including gastroscopy [EGD] and optical ileocolonoscopy [OC]). Furthermore, OGIB is classified as either overt OGIB (which manifests as recurrent melena or hematochezia) or occult OGIB (which presents by recurrent or persistent iron-deficiency anemia—IDA or positive fecal occult blood testing result or both) [1]. OGIB represents approximately 5% of all GI tract bleeding [2]; in these patients, the bleeding source is often located in the small bowel.

IDA occurs in 2%-5% of adult men and postmenopausal women in developed countries and is a common reason for referral to gastroenterologists [3]. According to the most recently published practice guidelines, upper and lower GI endoscopies are the cornerstone for the investigation of patients with IDA, particularly in postmenopausal female and all male patients. In these patients, EGD or OC identifies the cause of bleeding in 70%-80%; however, when both show negative results, the small bowel represents the target for further investigations [3].

The evaluation of these patients has been suboptimal for a long time, owing to the limitations of traditional imaging techniques. Therefore, the advent of a new and dedicated diagnostic tool, allowing a painless and accurate inspection of the entire small bowel (such as capsule endoscopy [CE]), was a major leap forward. In fact, the rapid accumulation of a substantial literature on CE in the past decade has led to a complete redesign of the diagnostic algorithms for patients with OGIB or IDA. Therefore, currently, all the guidelines issued by the major international gastroenterology-endoscopy societies confirm the primary role of CE in the diagnostic workup of patients with OGIB or IDA [1,3-7]. In the next few sections, we critically review the evidence supporting the use of CE in patients with OGIB and IDA, focusing our attention on the diagnostic workup preceding CE, on how CE compares with other modalities for the study of the small bowel, and on factors affecting CE accuracy.

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http://dx.doi.org/10.1016/j.tgie.2015.02.007
0049-0172/

2. Patients with OGIB: Where does CE fit?

Most articles on the evaluation of the small bowel (including articles on CE) report outcomes as diagnostic yield (DY), defined as the ratio of the number of positive result examinations to the number of all procedures. Conversely, only a few articles report efficacy measures—such as sensitivity, specificity, and predictive values (positive and negative) [8-10]—currently considered as the methodological cornerstones of any diagnostic tool. In our opinion, this is due to the lack of a reliable reference standard (RS) regarding the evaluation of the small bowel. An ideal RS should be able to assess (in a minimally invasive, comprehensive, effective, panoramic, and radiation-free manner) the entire length of the organ. At present, none of the available diagnostic tools fits all these requirements. Although intraoperative enteroscopy (IOE) is closer to the RS profile, it is invasive and has significant mortality and morbidity [11]. As the second best choice, device-assisted enteroscopy (DAE) could be considered as the RS examination for the small bowel. Nevertheless, it is relatively invasive, of high cost, is not readily available in most practice sites, and, for the purposes of a clinical study, it should be often performed with both per-oral and per-anal approach to allow the evaluation of the entire length of the small intestine [12].

It is also important to note that, in some studies, the DY is calculated by taking into consideration all the observed lesions, whereas in others clinically significant findings (P2 according to Saurin classification [13]) are considered as DY. Although categorizing CE findings with this classification represents a major effort to standardize CE reporting and answer the main clinical question of the relevance of any reported findings, significant subjectivity is still interwoven in this simplified probability grading [13]. Furthermore, reporting CE only as DY, that is, percentage of positive CE test results—hence ignoring the prognostic or clinical value of negative CE results—underestimates the overall contribution of the test in clinical practice. Recently, several studies have shown that patients with negative CE results have a significantly lower risk of rebleeding over time than patients with positive CE results [14-17]. These data suggest that in most patients with negative CE results, a "watchful waiting" approach may be a reasonable policy.

Nevertheless, despite the aforementioned limitations, DY represents the best available approximation parameter to measure the diagnostic performance of small bowel diagnostic tools, including that of CE. Therefore, all comparisons between CE and other diagnostic tools are mainly based on this parameter. This comparison should also take into account the safety profile of different examinations. In the setting of OGIB, CE appears extremely safe, and the reported rate of capsule retention (defined as the persistence of the capsule in the patient's body for more than 2 weeks) is approximately 1%-2% [4-7,18,19].

2.1. Patients with OGIB: Endoscopic workup before CE

In the setting of OGIB, the selection of patients referred to CE is mainly based on a negative prior bidirectional endoscopy result. However, although this is the prerequisite for a "proper" use of CE, international guidelines do not provide detailed recommendations on timing and quality of these examinations. Several studies report that, in patients with OGIB, CE shows bleeding lesions within the reach of conventional endoscopy in approximately 3%-17% and 2%-4%, in the upper and lower GI tract, respectively [20-23]. Vlachogiannakos et al [23] recently showed that there is a significant difference in the detection rate of non–small bowel lesions discovered by CE between patients referred from centers not performing CE and those undergoing both EGD and CE in the same center (6.3% and 1.2%, respectively, $P = 0.026$). These data may support the hypothesis that it may be worthwhile to systematically repeat both upper and lower endoscopies in the centers where CE will be performed. However, an Australian study [24] in which EGD and colonoscopy were repeated, whenever they had been nondiagnostic more than 6 months before CE, did not show a significant number of lesions missed on previous examinations. In addition, if we consider the issue from an economical point of view, the systematic repetition of EGD and OC does not seem to be cost-effective. For these reasons, currently, the choice of repeating upper or lower GI endoscopy in patients referred to CE should be made on an individual case-by-case basis.

2.2. Patients with OGIB: CE or radiological tests?

Current guidelines, which recommend that CE should be performed as the first test in patients with OGIB, after negative EGD and OC results, are supported by moderate- to high-quality evidence mostly from large observational studies, which showed a superior DY of CE, when compared with both radiological and endoscopic tests.

Triester et al [25] conducted a meta-analysis of studies comparing CE with small bowel barium radiography (small bowel follow-through or enteroclysis). They found that the CE DY for all findings was 67%, compared with 8% observed in patients undergoing radiological examinations ($P < 0.01$). When the DY was restricted to "clinically significant findings" it was shown to be 42% for CE and 6% for small bowel barium radiography ($P < 0.001$). More recently, Laine et al [26] published a study that casts some doubts on the superiority of CE over radiological methods, particularly when established clinical outcomes are considered. The authors reported on 136 patients (54 overt and 82 occult OGIB), who were randomly assigned to CE or small bowel contrast radiography. Interestingly, although the DY was 30% with CE and 7% with small bowel radiography, the primary study end point (the rebleeding rate) was not statistically different between the 2 groups (30% in patients undergoing CE and 24% in those investigated with radiology). Furthermore, the need for any subsequent diagnostic or therapeutic procedures, hospitalizations, and transfusions was equivalent. However, the therapeutic workup after a positive small bowel examination result was not standardized. Hence, in this article, the discrepancy between clinical outcomes and the DY is more likely to reflect the current limitations in treating small bowel lesions than the ability to diagnose them. Moreover, approximately 40% of patients were enrolled owing to overt GI bleeding, which represents an independent risk factor for rebleeding [14,27]. In addition, other authors [28,29] have underscored that the cause of bleeding influences the outcome, albeit in the present study all the possible lesions were considered together.

However, the major criticism to these studies [25,26] is in regard to the test used as the CE "comparator." Old radiological tests (ie, small bowel follow-through and small bowel enteroclysis), based on radiopaque contrast agents and radiological equipment with low spatial resolution, are certainly a suboptimal comparator option. However, new radiological methods have been introduced in clinical practice. These are based on computed tomography (ie, computed tomographic enterography [CTE]) or magnetic resonance (ie, magnetic resonance enterography) techniques that, by combining intravenous and per-oral contrasts agents, are able to provide detailed images of the small bowel, ensuring high spatial resolution. Interestingly, studies comparing CE with these new-generation radiological tests have yielded conflicting results.

In 2004 Hara et al [30] retrospectively evaluated 19 patients with OGIB receiving both CE and CTE; they found a significantly higher DY for CE (DY of CE and CTE: 63% and 21% respectively; $P = 0.020$). These data have been recently confirmed by He et al [31], comparing CE with a 64-slice multiphase CTE (DY of CE and CTE