

Investigating obscure gastrointestinal bleeding: capsule endoscopy or double balloon enteroscopy?

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ABSTRACT

The possibility to visualise the small bowel has dramatically improved with the introduction of capsule endoscopy (CE) and double balloon enteroscopy (DBE). CE and DBE have become standard practice in investigating suspected diseases of the small bowel. An important reason to perform small bowel investigations is obscure gastrointestinal bleeding. To investigate obscure gastrointestinal bleeding, some advocate performing CE while others recommend DBE. In this systematic review, we provide an overview of studies in which patients with obscure gastrointestinal bleeding underwent both CE and DBE. These data show that CE and DBE have comparable diagnostic yields in the evaluation of obscure gastrointestinal bleeding of 50 to 60%. Therapeutic interventions using DBE were performed in 11 to 57% of cases. In most studies, there was good concordance between the two procedures but both techniques can be falsely negative. Given its safety, patient tolerability and ability to view the entire small bowel, CE can be recommended as the first investigation for obscure gastrointestinal bleeding, if necessary, followed by DBE. Finally, we provide an algorithm with practical guidelines for the evaluation of obscure gastrointestinal bleeding.

KEYWORDS

Capsule endoscopy, double balloon endoscopy, double balloon enteroscopy, gastrointestinal bleeding

INTRODUCTION

Obscure gastrointestinal bleeding is defined as bleeding from the digestive tract that persists or recurs

without an obvious aetiology after a normal oesophago-gastroduodenoscopy and colonoscopy.¹ It can be categorised into overt and occult obscure gastrointestinal bleeding based on the presence or absence of clinically evident bleeding. Approximately 5% of patients presenting with gastrointestinal bleeding have no identified source on upper endoscopy and colonoscopy.¹ The cause of obscure gastrointestinal bleeding is usually a lesion located in the small bowel, but also includes lesions that were overlooked during conventional endoscopy, either because of intermittent bleeding or truly missed lesions. An often occurring dilemma in obscure gastrointestinal bleeding is whether to undertake invasive investigations or to take a conservative supportive approach (stopping NSAIDs, supplementing iron, or blood transfusion). The investigation of obscure gastrointestinal bleeding has been revolutionised by the introduction of capsule endoscopy (CE) and double balloon enteroscopy (DBE).² Until recently, erythrocyte scintigraphies and angiography were proposed for patients with obscure gastrointestinal bleeding and *active* bleeding, and repeat endoscopies, push-enteroscopy, enteroclysis and small bowel series were recommended in patients with obscure gastrointestinal bleeding and *occult* bleeding.³ Over the last years, CE has proven to be superior to all of these diagnostic modalities in the evaluation of obscure gastrointestinal bleeding.⁴⁻⁹ In addition, CE has a high negative predictive value. An important limitation of CE is the inability to obtain histology and to perform therapeutic interventions. A technique that has proven to be of complementary value is DBE. This method, introduced in 2001, is based on the combined use of a balloon-loaded enteroscope and a similarly balloon-loaded overtube.¹⁰ Alternately inflating and deflating the balloons

and straightening the endoscope with the overtube achieves a stepwise progression of the enteroscope throughout the small bowel. DBE can be carried out through the antegrade (oral) or the retrograde (anal) route. With a combined antegrade and retrograde approach a complete small bowel examination can be achieved in up to 86% of patients.^{11,12} Endoscopic interventions such as mucosal biopsy, argon plasma coagulation, polypectomy and balloon dilation can be performed. However, DBE is an invasive and time-consuming procedure and there is a considerable risk of complications such as pancreatitis or perforations, especially in therapeutic procedures.¹³

An important question for the clinician is how to proceed in the evaluation of obscure gastrointestinal bleeding after normal initial investigations. It is unclear how the new diagnostic and therapeutic strategies should be incorporated in our current armamentarium. Following a normal gastroduodenoscopy and colonoscopy, should the next step be CE or DBE? To answer this dilemma, we performed a systematic literature search on studies in which CE was compared with DBE in patients with obscure gastrointestinal bleeding.

METHODS

A systematic literature PubMed search was performed using the search terms 'capsule endoscopy' and 'double balloon enteroscopy', 'double balloon endoscopy' or 'push-and-pull enteroscopy'. Only articles in which patients with obscure gastrointestinal bleeding had undergone both techniques, and of whom information regarding the findings was provided, were included. Only full-text articles in the English language published between 2000 and 31 December 2008 were included. Reference lists of identified articles were reviewed.

RESULTS

Our results retrieved nine articles, which are summarised in *table 1*.¹⁴⁻²³ Seven of these articles were prospective studies. We also included two retrospective studies, because of their large number of patients. The number of patients in these studies varied between 13 and 74. Mean age of patients was around 60 years in almost all studies. Most studies included both patients with obscure-overt and obscure-occult gastrointestinal bleeding.

Technical characteristics

In all studies except one, DBE was performed following CE; Matsumoto *et al.* used the reverse order of procedures.¹⁴ In one study, all patients underwent both an antegrade as well as a retrograde DBE procedure,²⁰ whereas in the other studies the DBE strategy varied. In three of these studies, the antegrade or retrograde approach of DBE was chosen based on the time a lesion was seen on CE in relation to the small-bowel transit time of the capsule.^{18,19,23} Two studies chose the route of DBE depending on the findings of CE without providing further details²² or depending on the medical history.¹⁶ One study chose the antegrade route of DBE in all cases, followed by the alternate approach if considered necessary.¹⁵ Only one study attempted complete small bowel examination with both antegrade and retrograde DBE in all patients.²⁰ In many studies, the decision to perform an additional DBE using the alternate route was made after considering several factors, including the results of the initial procedure, clinical indication and patient consent.^{15,16,18,19} Only two studies had a single-blinded design, i.e. the endoscopist performing the DBE was unaware of the results of the CE.^{16,21}

Diagnostic yields of CE and DBE

The diagnostic yields of CE and DBE for obscure gastrointestinal bleeding varied between 38 and 83%

Table 1. Overview of studies on capsule endoscopy (CE) and double balloon enteroscopy (DBE) in obscure gastrointestinal bleeding

Author (reference)	n	Age (mean)	Design	Overt/occult	Diagnostic yield CE (%)	Diagnostic yield DBE (%)	Concordance (%)
Matsumoto ¹⁴	13	48	Prospective	13/0	38	46	92
Hadithi ¹⁵	35	63	Prospective	22/13	80	60	74
Nakamura ¹⁶	32	59	Prospective, single-blinded*	32/0	59	43	29
Ohmiya ¹⁷	74	Data missing	Retrospective	Data missing	50	53	73
Kaffes ¹⁸	60	62	Prospective	34/26	83	75	65
Fujimori ¹⁹	45	60	Prospective	Data missing	40	50	89
Kamalaporn ²⁰	51	64	Prospective	14/37	Data missing	Data missing	Data missing
Kameda ²¹	32	62	Prospective, single-blinded	26/6	72	66	50
Arakawa ²²	74	Data missing	Retrospective	Data missing	54	64	80

*The endoscopist performing the double-balloon enteroscopy was unaware of the result of the preceding.

for CE, and between 43 and 75% for DBE. Considering all studies together, the most frequent diagnosis was angiodysplasias, followed by tumours and ulcerations/erosions. The diagnostic yield was higher in overt gastrointestinal bleeding than in occult gastrointestinal bleeding.²² The diagnostic yields of both DBE and video capsule endoscopy (VCE) for ongoing overt bleeding were significantly higher than those of previous overt and occult bleeding (87 vs 52% using DBE, and 88 vs 48% using CE).²² Therapeutic interventions using DBE were performed in 11 to 57% of cases. These included electrocoagulation of angiodysplasias and radiation enteritis, applying haemo-clips in Dieulafoy's lesions, endoscopic mucosal resections of polyps and balloon dilation of strictures.

Concordance between CE and DBE

In most studies, DBE confirmed the findings of CE in the majority of cases. The concordance between findings of CE with those of DBE varied between 29 and 92% (table 1). However, in almost every study, several lesions that were detected by DBE had been missed by CE, and vice versa. Lesions missed by CE but identified by DBE included angiodysplasias,^{15,17,19,21} ulcers,^{17,18,21} small bowel diverticula,^{16,19,21} gastrointestinal stromal tumour (GIST),^{17,19} malignant lymphoma,¹⁹ leiomyosarcoma,¹⁹ enteric tuberculosis,¹⁹ varices¹⁷ and colorectal cancer.¹⁶ In the largest series published so far, in 162 patients with obscure gastrointestinal bleeding, of whom 74 underwent both VCE and DBE, Arakawa found 11 DBE positive cases where VCE was normal.²² These concerned cases of varices in a Roux-en-Y loop, varices elsewhere in the small bowel, angiodysplasias, a Dieulafoy's lesion, a GIST, a Meckel's diverticulum, a lipoma and a colon carcinoma. Similarly, there were lesions detected by CE that were not confirmed at DBE. These included angiodysplasias,^{15,17,19,21,22} GIST,^{17,22} a submucosal tumour,^{14,16} polyps,¹⁵ erosions²¹ and varices.¹⁷

Finally, in some studies, CE identified lesions that were within the reach of conventional endoscopy. These included cases of colorectal cancer,²² duodenal varices,²² gastric antral vascular ectasia,¹⁹ colonic diverticula¹⁹ and oesophageal varices.¹⁹

Completion rates and complications

The entire small intestine was more often visualised by CE compared with DBE in most studies.^{14,16,17,21} In the study by Arakawa *et al.*, complete small bowel investigation was achieved by DBE and CE with similar success rates (70 and 68%, respectively).²² However, in this study, total enteroscopy by DBE combining the oral and anal route was attempted in only about half of the cases.²²

In all studies, complication rates were low. Capsule retention occurred in up to 5% of cases.²² In most of these cases, the lodged capsule could be removed by DBE,

thereby preventing surgery. Minor complications after DBE included abdominal pain, nausea, a painful throat or mucosal injury due to contact with the overtube.^{17,19,21} In the largest study, major complications for DBE included pancreatitis (1.7%) and perforations (0.8%).¹⁷ DBE was considered more painful than CE by patients.¹⁵ Finally, it must be noted that a small number of patients did not undergo DBE at all due to severe cardiopulmonary comorbidity or thrombocytopenia.^{17,21}

Outcome and follow-up

All but two studies included a follow-up period. The mean duration of follow-up varied from 5 to 19 months.^{15-19,21,22} Re-bleeding rates were calculated in most of these studies and varied from 5 to 20%.

In the largest series published to date, none of the cases with normal findings on CE and/or DBE experienced re-bleeding.²² Contradictory results were obtained by Fujimori *et al.*, who found that the re-bleeding rate was 5% in patients with positive diagnoses on CE and/or DBE, and 12% in normal cases.¹⁹

Small-bowel vascular lesions seem to be more prone to re-bleeding than small-bowel nonvascular diseases.²² This has also been observed by others.¹⁷ The presence of comorbidity, especially portal hypertensive disease and chronic renal failure and severe anaemia at presentation were factors associated with an increased risk of re-bleeding.²²

After combined use of CE and DBE, blood transfusions were needed during the follow-up period in 0 to 20% of cases.²² In one study, the number of patients requiring blood transfusions decreased from 57% before small bowel investigations to 17% after combining CE and DBE.¹⁸

DISCUSSION

In this paper, we reviewed the use of CE and DBE in the evaluation of obscure gastrointestinal bleeding. We found a wide variety in reported diagnostic yields of CE and DBE, which can be explained by several factors. First, different definitions of diagnostic yield existed. In some studies, every abnormality detected by CE or DBE was included in the diagnostic yield, whereas in others only possible sources of bleeding were considered diagnostic. In addition, the timing of CE has shown to be of importance. The yield of CE in patients with obscure gastrointestinal bleeding was 91% if performed within two weeks after the initial bleeding, compared with 34% in patients undergoing CE thereafter.^{23,24} Next, several studies indicate that the diagnostic yields of CE and DBE are higher in obscure-overt than in obscure-occult bleeding. Given that the proportion of patients with obscure-overt and obscure-occult bleeding differed between studies, this

may have contributed to the variety in reported diagnostic yields. It must also be realised that in some studies, DBE was performed with the combination of the antegrade and retrograde approach, whereas in others only one approach was chosen, leading to major differences in the proportion of complete small bowel examination with DBE between studies. However, taking all data together, the diagnostic yield seems comparable between CE and DBE for the evaluation of obscure gastrointestinal bleeding.

The major drawback of CE is the inability to obtain histological samples or perform therapeutic interventions. The role of DBE is a complementary, therapeutic one, providing endoscopic therapy of bleeding sites in the small bowel. The percentage of cases in which therapeutic interventions using DBE were performed, the therapeutic rate, varied between 11 and 57%. This variation may be due to different definitions of therapeutic procedures. In most studies, this was defined as the proportion of cases in which endoscopic intervention was performed. In other studies, establishing a histopathological diagnosis or marking tumours or diverticula for surgery were also considered therapeutic procedures.

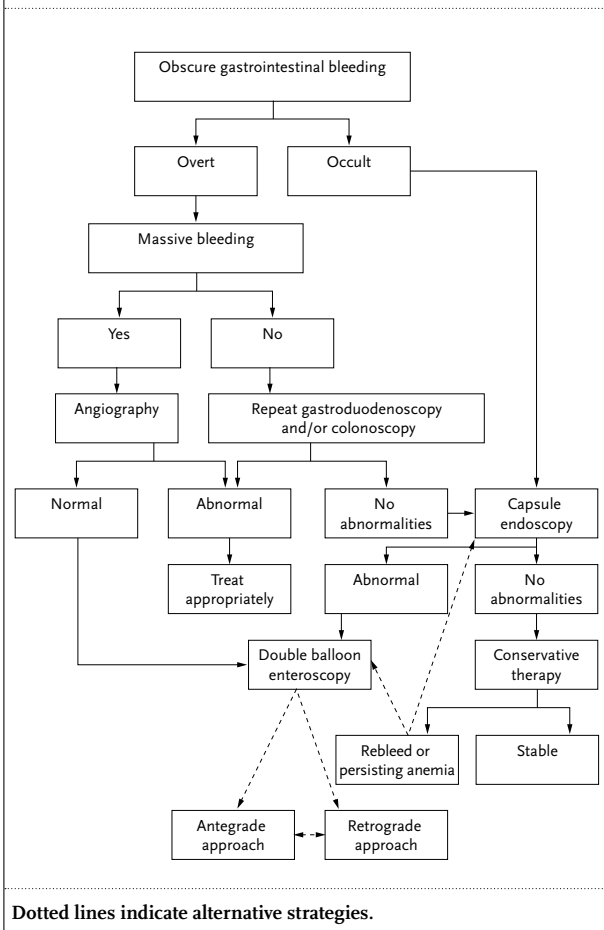
Given the comparable diagnostic yield of CE and DBE in the evaluation of obscure gastrointestinal bleeding, how should these investigations be incorporated in clinical practice? CE is relatively patient-friendly, minimally invasive, safe and usually performed on an outpatient basis. DBE is relatively labour intensive, usually involves one endoscopist and two nurses, requires the use of sedation, is more painful and invasive for the patient and has a larger risk of complications compared with CE. With respect to the cost-effectiveness of these procedures, two studies are available.^{25,26} Both reports used models comparing five different management strategies of obscure gastrointestinal bleeding including CE and DBE, although these strategies were not exactly similar in the two studies. Nevertheless, both reports indicate that DBE is the most cost-effective approach for the evaluation of obscure gastrointestinal bleeding.^{25,26} However, in both papers it is suggested that CE-guided DBE may be associated with better long-term outcomes because of the potential for fewer complications and decreased utilisation of endoscopic resources. This concept of CE as a way to select patients for DBE, and helping to direct whether the oral or anal approach should be used, has been studied in clinical practice.²⁷⁻²⁹ Such a strategy has shown to generate a diagnostic yield of DBE of up to 83%²⁹ and a therapeutic yield of up to 69%.²⁹ With this strategy, CE is used for the initial diagnosis and DBE for histopathological confirmation of the diagnosis and, if technically possible, endoscopic therapy. One could consider deviating from this strategy in emergent cases with massive bleeding, where DBE should be selected over CE, to prevent delay in endoscopic therapy.

Another important question is how patients with a normal CE are best managed. Most studies indicate that re-bleeding rates and need for transfusions are low after normal CE.³⁰ Consensus emerges that patients with obscure-occult GI bleeding and a normal CE are probably best managed conservatively without further investigations.³¹ Examples of conservative management are a 'wait and see' policy, cessation of NSAIDs, iron supplementation or blood transfusions. Nevertheless, if a patient has repeated overt bleeding and/or continues to be transfusion dependent, two options seem reasonable. One could repeat a CE procedure or perform a DBE. In a study in 24 patients with obscure gastrointestinal bleeding and a normal CE, repeat CE revealed abnormal findings in 75% of cases.³² In another series of 20 patients, a second CE procedure revealed significant pathology in 35% of cases.³³ Alternatively, DBE could be performed after an initial normal CE. It seems reasonable to start with the antegrade approach, given that the depth of insertion is larger compared with the retrograde approach, and the fact that the majority of abnormalities are located in the proximal small bowel. Indeed, such an approach in four patients with obscure gastrointestinal bleeding and normal CE revealed a diagnosis in all cases.³⁴ In *figure 1*, we propose an algorithm incorporating CE and DBE in the evaluation of obscure gastrointestinal bleeding. In patients with massive overt bleeding, a CT angiography or conventional angiography should be considered. Especially in patients with obscure-overt bleeding, we suggest repeating conventional endoscopies. As the next step, we recommend CE as the preferred diagnostic procedure in obscure gastrointestinal bleeding, based on its safety, patient tolerance and ability to view the entire small bowel. DBE should be considered in patients with a positive finding on CE requiring endoscopic evaluation and in cases with massive bleeding with a normal CT angiography. The route of insertion for DBE should be guided by the medical history or the findings of CE. If needed, the alternative route may be chosen. In patients in whom small intestinal bleeding is suspected despite a normal CE, for example those with unexplained refractory or recurring anaemia, a repeat CE procedure could be considered or, alternatively, a DBE.

CONCLUSION

The possibility of visualisation of the small bowel has dramatically improved with the introduction of CE and DBE and they have rapidly become standard practice in investigating diseases of the small bowel. The procedures can be considered complementary rather than competing techniques. In suspected small bowel bleeding, CE should be used for the initial diagnosis and, if necessary, DBE for histopathological confirmation of the diagnosis and, if technically possible, endoscopic therapy.

Figure 1. Algorithm with guidelines on the use of capsule endoscopy and double balloon enteroscopy for the evaluation of obscure gastrointestinal bleeding



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