Factors Predicting the Diagnostic Yield and Intervention in Obscure Gastrointestinal Bleeding Investigated Using Capsule Endoscopy

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Abstract

Background: In patients with obscure gastrointestinal bleeding (OGB), capsule endoscopy (CE) is the investigation of choice after negative conventional endoscopy. However, there is paucity of data on which clinical factors predict the ability of CE to detect pathology and alter management.

Aim: To investigate clinical factors which predict a higher diagnostic yield and a change in management in patients presenting with OGB.

Methods: Data was collected in patients with OGB for type of OGB [overt (OB) or iron deficiency anaemia (IDA)], co-morbidity, use of anticoagulants, transfusion dependence, subsequent CE diagnosis and follow up data. Factors that predicted a higher yield and a change in management were identified using logistic regression.

Results: There were 427 patients (IDA 74%) with a mean age of 58 years (range 17-92). The diagnostic yield was 50% with a change in management in 30% of patients. The commonest finding was angiodysplasia in 52% of patients. There was no significant difference in the diagnostic yield between the two groups (OB: 56%, IDA 48%, p=0.15). On logistic regression, age (p=0.001), the use of warfarin (p=0.02) and liver co-morbidity (p=0.001) were significant factors which predicted a higher yield with CE. Factors which predicted a change in management included the presence of co-morbidity (p=0.02) and having a diagnosis of angiodysplasia on CE (p=0.001). Conclusion: This is a large series of CE in OGB. Increasing age, anti-coagulation and liver co-morbidity are significant predictors of a positive diagnostic yield whilst the presence of co-morbidity or a diagnosis of angiodysplasia may predict a change in management.

Key words

Capsule endoscopy – obscure gastrointestinal bleeding – angiodysplasia.

Introduction

Capsule endoscopy (CE) is a new method for investigating the small bowel which has revolutionised the field of endoscopy [1]. Obscure gastrointestinal bleeding (OGB) is a common diagnostic challenge faced by gastroenterologists. It occurs in approximately five percent of cases and is defined as persistent/recurrent gastrointestinal bleeding where conventional endoscopy is negative and a small bowel source is suspected [2-4]. OGB is sub classified as overt with the presence of melaena or haematochezia or occult with anaemia and/or positive faecal occult blood testing [5].

Studies using CE have shown a high diagnostic yield in the context of OGB when compared to conventional modalities of investigation [6, 7]. It now has an established role in the management of OGB after negative conventional endoscopy [2, 6, 8]

There is however limited published data on which clinical factors predict the ability of CE to detect pathology in routine practice [6, 9-11]. Increasing age has been associated with a higher diagnostic yield [9]. Whilst some studies have suggested that the yield is higher in patients who have overt bleeding than those with obscure bleeding [9-14], these findings have not been mirrored in all studies. In addition, there is paucity of data on factors which can predict outcome after CE. One small study (n=56) showed that a lower median haemoglobin, the requirement for transfusion, reduced general condition of the patient and positive findings on CE were associated with a change in management of patients [12]. Also, despite angiodysplasia being the commonest finding in most of these studies [9, 11, 12, 15], the benefit of treating these lesions remains debatable [16]. Thus, if the outcome after CE could be predicted, it might be possible to target patient groups that might benefit from CE and avoid unnecessary investigations in the high risk groups with potentially untreatable lesions.
This study evaluates the clinical utility of CE in patients presenting with OGB in a single tertiary institution in the UK. It investigates which clinical parameters predict a higher diagnostic yield and factors that have an impact on patient management. This study tests the hypothesis that CE should be reserved for a selected group of patients with treatable lesions.

Methods

Patients

Sheffield Teaching Hospitals (STH) comprises two tertiary hospitals (Royal Hallamshire Hospital 860 beds and the Northern General Hospital 1100 beds) in the South Yorkshire Region of the United Kingdom (UK) which serves a population of 2 million. All 427 consecutive patients referred for CE for suspected small bowel bleeding since the set up of the service in June 2002 to February 2008 were included. All patients had undergone gastroscopy and colonoscopy which had not detected the source of bleeding, prior to CE.

Data collected included type of OGB [overt (OB: melena/haematochezia) or occult/ iron deficiency anaemia (IDA)], demographics, co-morbidity (stratified into cardiovascular disease, respiratory disease, renal disease, haematological disease, liver disease, rheumatological disease and present malignancy), use of anticoagulants, non steroidal anti-inflammatory drugs (NSAID’s), transfusion dependence (defined arbitrarily as three or more transfusions over 12 months) and CE diagnosis. Follow up data and subsequent change in management were obtained from hospital records and the referring physician. The duration of follow up for patients varied due to the availability of the relevant information.

The data was analyzed using the Statistical Software Package version 15.0 (SSPS Inc, Chicago, IL). Chi squared tests were used to compare diagnostic yields between the two groups (OB/IDA). A p value <0.05 was deemed statistically significant. Logistic regression was performed to identify factors that predicted a higher yield and a change in management with CE.

Capsule endoscopy

The Pillcam SB (Given Imaging Ltd, Yoqneum, Israel) which is well reported in the literature was used in this study [1]. Patients were fasted overnight for 12 hours after ingestion of two sachets of polyethylene glycol solution (Kleen-Prep, Norgine). Written informed consent was obtained from all patients. Patients were allowed to drink 2 hours after and eat a light snack 4 hours after ingestion of the capsule. The sensor array and recorder pack were disconnected after eight hours and images were downloaded onto a workstation. The latter 120 cases were examined 30 minutes after capsule ingestion using the Real Time Viewer (Given Imaging Yoqneum Ltd) and given metoclopramide intramuscularly if the capsule remained in the stomach. All videos were analysed by an experienced Consultant Gastroenterologist (MEM) who was blinded to the indication for CE.

The diagnostic yield was defined as the number of clinically significant lesions thought to be the source of the OGB in the entire cohort. Significant lesions included vascular lesions such as angiodysplasia, large ulcers, tumour or varices. insignificant findings that were not included in the diagnostic yield included red spots or isolated small angiodysplasia with no evidence of bleeding, single/ isolated erosion or non bleeding diverticulae. The presence of fresh bleeding (without a definitive lesion) was deemed contributory to the diagnostic yield. For the purpose of this study, a diagnosis of Crohn’s disease was made in patients with OGB who had evidence of multiple ulcers or erosions (minimum 5), mucosal oedema and erythema with a negative history for NSAID ingestion. Arbitrary patients with large isolated ulcers were categorised as small bowel ulcers as they might be due to alternative localised disease processes. Small infrequent erosions were not deemed pathological as they can occur in healthy subjects [17].

Results

Patients

There were 427 patients with a mean age of 58 years (range 17-92), 43% of referrals were from outside the region. IDA comprised 74% of the referrals (n=316) whilst 26% (n=111) were patients with OB. Thirty nine percent of patients had at least one co-morbidity present. Eight percent of patients (n=34) were on warfarin and 9.8% (n=42) were on NSAIDs/ aspirin. Whilst eight percent (n=34) of patients were transfusion dependent, 26% (n=110) had had a previous transfusion for their OGB. Six percent of CE (n=25) were performed as an inpatient setting. The mean follow up in all patients was 17 months (range 1-32 months).

Diagnoses and factors predicting yield

The overall diagnostic yield was 50% in all patients with OGB (n=213). There was no significant difference in the diagnostic yield between the two groups (OB: 56%, IDA 48%, p=0.15). The diagnosis found in all patients is tabulated in Table 1. Figure 1 shows the diagnoses and age distribution.

In the majority of patients with a positive yield, lesions identified were within the small bowel; however 9.4% (n=20) of the lesions found were in the gastro-duodenum whilst 2.3% (n=5) were in the colon. These included peptic ulcer disease (n=5), gastric antral vascular ectasia/GAVE (n=9), angiodysplasia of the stomach or colon (n=5), bleeding oesophageal polyp (n=2), gastric varices (n=2), caecal ulcer (n=1) and haemorrhoids (n=1).

The single largest diagnostic group were those with small bowel angiodysplasia in 52% of patients (n=110). The majority of these presented with IDA, but as many as 26% presented with overt bleeding. The mean age for patients with a diagnosis of angiodysplasia was 67 years (range 27-90 years). Detailed analysis of the latter 70 of these 110 patients in this cohort revealed that the majority of lesions (49%) were within the proximal small bowel and within an hour of the pylorus. In 20% the lesions were judged to be
within the mid small bowel and a further 20% within the distal small bowel. In 11% of patients, the angiodysplasia was in more than one area of the small bowel. On multiple logistic regression analysis, increasing age (p<0.001) and the presence of co-morbidity (p=0.008) were associated with a diagnosis of angiodysplasia.

**Table I.** Diagnosis found in patients with obscure gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Iron deficiency anaemia (total n=316)</th>
<th>Overt gastrointestinal bleeding (total n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients with each diagnosis</td>
<td>Number of patients with each diagnosis</td>
</tr>
<tr>
<td>Small bowel angiodysplasia</td>
<td>81</td>
<td>29</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Small bowel tumours</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Small bowel ulcers</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Fresh bleeding</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastric/ small bowel varices</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Polyps</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding small bowel diverticulae</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel Dieulafoy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel strictures</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Caecal angiodysplasia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastric angiodysplasia</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Five of these patients were on NSAIDS which were thought to be the underlying aetiology.

Small bowel tumours accounted for 3% of diagnoses (n=13). Patients were equally likely to present with IDA (n=6) or OB (n=7). Diagnoses included gastrointestinal stromal tumour (4), carcinoid (1) adenocarcinoma (3), haemangiomia (4), metastatic renal cancer (1). The mean age of these patients was 47 years (range 20-72 years, Figure 1). In one patient with incomplete examination of the small bowel by CE, an additional small bowel tumour was subsequently resected at laparotomy following a further significant episode of OB.

Coeliac disease was diagnosed in 2% (n=8) of patients. These patients, who had been referred for CE for investigation of recurrent anaemia, had had either negative/ equivocal initial duodenal histology with positive coeliac serology. Mucosal changes seen at CE (for example mucosal atrophy, mosaic pattern, scalloping of folds) resulted in these patients undergoing repeat duodenal biopsy to revisit the diagnosis of coeliac disease which was subsequently confirmed with repeat histology.

On univariate analysis the presence of co-morbidity (p=0.001, OR 2.1, 95% CI 1.4-3.2) particularly cardiovascular (p=0.001, OR 2.4, 95% CI 1.5-3.9), renal (p=0.02, OR 4.2, 95% CI 1.2-15) or liver disease (p=0.01, OR 2.6, 95% CI 1.2-5.6) were significant factors which predicted a higher yield with CE. On multiple logistic regression age (p=0.001), the use of warfarin (p=0.001, OR 3.6, 95% CI 1.6-8.1) and patients who were transfusion dependent (p=0.01, OR 2.6, 95% CI 1.2-5.6) were significant factors which predicted a higher yield with CE. On multiple logistic regression age (p=0.001), the use of warfarin (p=0.02) and liver co-morbidity (p=0.001) remained significant. The diagnoses found in patients on warfarin or with liver co-morbidity is tabulated in Table II.

**Change in management**

In thirty percent of patients who underwent CE (n=126), management was altered. This was mainly in the form of application of argon plasma coagulation (APC) to small bowel (n=60), colonic angiodysplasia (n=3) or gastric

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Crohn’s disease was found in 13 patients presenting with isolated OGB without other associated symptoms. The majority of patients (85%) had presented with IDA. Small bowel ulcers of uncertain aetiology were found in 5% (n=20).

![Fig 1. Diagnoses at capsule endoscopy in relation to age. PUD: peptic ulcer disease; SB: small bowel; AG: angiodysplasia; GAVE: gastric antral vascular ectasia; N: normal](image-url)
angiodysplasia (n=2) and gastric antral vascular ectasia (n=9) in 59% of patients. Twelve percent of patients (n=15) were referred for surgery. This included laparotomy for tumour removal (n=10), resection or sewing of angiomata (n=2) and resection of either idiopathic strictures (n=2) or Crohn’s disease (n=1) and laparoscopy for intestinal endometriosis (n=1). Table III shows the change in management in all patients.

Table II. Diagnosis found in patients with liver co-morbidity and patients on warfarin

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with liver co-morbidity (n= number of patients)</th>
<th>Patients on warfarin (n=number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiectasia</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Varices/Portal hypertensive gastropathy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic renal cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel stricture</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Polyp</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table III. Change in management in patients with obscure gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Change in management</th>
<th>Number of patients (total n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application of Argon Plasma Coagulation for angiodysplasia or gastric antral vascular ectasia</td>
<td>74</td>
</tr>
<tr>
<td>Surgery</td>
<td>15</td>
</tr>
<tr>
<td>Injection of ulcer</td>
<td>2</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory bowel disease directed therapy</td>
<td>7</td>
</tr>
<tr>
<td>Polypectomy</td>
<td>3</td>
</tr>
<tr>
<td>Enteroscopy &amp; biopsy</td>
<td>11</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>11</td>
</tr>
</tbody>
</table>

Miscellaneous: Gluten free diet (2), avoided surgery (1), Helicobacter eradication (4), stopping NSAIDs (1), repeat OGD/flexible sigmoidoscopy (2), Ultrasound doppler of portal veins and propanolol (1)

On logistic regression, factors which predicted a change in management in patients included the presence of co-morbidity (p=0.02) and having a diagnosis of angiodysplasia on CE (p=0.001). In association with this, transfusion dependence was also more likely in those with co-morbidity (p=0.009, OR 2.795% CI 1.3-5.6), on warfarin (p=0.001, OR 5.295%CI 2.2-12.6), increasing age (p<0.001, OR 4.995% CI 2.0-12) and in patients with a diagnosis of angiodysplasia (p=0.016, OR 2.595% CI 1.2-5). In contrast, the presentation of OGB (IDA/OB) did not have an effect on the likelihood of a change in management in patients (p=0.38).

Incomplete examinations

In 4.2% (n=18), the capsule did not enter the colon at the end of 8 hours and in 2.8% small bowel examination failed due to delayed gastric emptying of the capsule (n=10) or failed transmission (n=2). One retained capsule was found at laparotomy at time of resection of an idiopathic stricture.

Discussion

This is a large reported series of patients with OGB, which confirms that the high diagnostic yield of CE found in clinical trials translates well to routine clinical practice. A yield of 50% compares very favourably with the yield of radiological methods [18, 19] and push enteroscopy [20-22]. It avoids the risk of radiation exposure, of endoscopic- and sedation-related complications and is preferred by patients [23]. The only complication in this series of 427 patients was a single capsule retention in a patient with idiopathic stricture, undetected by prior radiological investigation, which required resection.

The largest single diagnostic group is that of angiodysplasia, consistent with other studies [9, 11, 12, 15]. We have also confirmed, however, that this diagnosis is associated with increased age and co-morbidity, and indeed is by far the commonest finding in those over 50 years of age. This is perhaps not unexpected: angiodysplasia is known to be more common in the elderly and is also associated with renal disease [24]. What the CE literature adds to historical knowledge, however, is the fact that this is no longer considered to be primarily a disease of the colon.

If the largest cohort is composed of elderly, frail patients with angiodysplasia, the question arises as to whether or not they benefit from investigation. Sedation- and endoscopic complications are less well tolerated by those with significant comorbidity and the treatment of angiodysplasia is neither straightforward nor always successful [16, 25]. Medical treatment with hormonal therapy has not proven effective [16], the use of thalidomide is based on case series only [16, 26] and endoscopic therapy at best demonstrates a reduction in blood transfusion rate rather than cure [21, 27]. Specific treatment of these lesions may not be the only way in which patient management was affected, however. Simply having a positive diagnosis may save the patient from repeated fruitless endoscopic and radiological investigations for bleeding lesions.

The reason these patients are the largest cohort is that they represent the greatest clinical challenge. The choice to investigate further seems likely to have been dictated by the effect on the patients’ quality of life, of which transfusion dependency, more common in older patients, those with co-morbidity and angiodysplasia, might be considered a surrogate marker. Certainly, the transfusion dependency is likely to have a wider impact on the patient, with more visits and increased time in hospital and possibly a greater number of investigations.

Furthermore, co-morbidity and a diagnosis of angiodysplasia were factors that predicted a change in management, which was made in 30% of our cases. As almost half the angiodysplasias were within reach of a push
enteroscopy, most were endoscopically treated, with some being medically treated and very few submitted to double balloon enteroscopy or surgery. Further studies are needed to assess the impact of medical and endoscopic therapy on small bowel pathology, particularly angiodysplasia.

In this study, CE had a positive impact on subsequent management in 30% of patients. However, the lack of data on transfusion requirements and haemoglobin measurements post CE and the difference in the follow up duration of patients does not allow us to comment on the effect of CE in long term outcomes. Capsule endoscopy is purely a diagnostic test; improvements in bleeding parameters are not directly attributed to CE but to the definitive therapy which CE directs clinicians to, which we have alluded to, in 30% of our cohort. In addition, the findings of this study would have been further strengthened if data on other clinical factors such as relationship between time of bleeding episode to CE and mean haemoglobin levels were included.

Other studies (including our own earlier data) suggest a greater yield in patients with overt rather than occult bleeding [6, 9, 14]. However this must be called into question when such a large series fails to confirm an association. Transfusion dependence, a predictor of diagnostic yield in other studies was only associated with a diagnosis on univariate analysis in this series [9, 12, 28]. Interestingly, as well as increasing age, warfarin therapy and chronic liver disease predicted a positive diagnostic yield using CE, angiodysplasia and GAVE being the commonest diagnoses in the latter two categories. These vascular abnormalities may be more common in patients taking warfarin because of their known association with cardiac diseases, often the indication for anticoagulation [29]. These vascular abnormalities have also been a reported finding in patients with chronic liver disease and abnormal clotting [30-32].

A proportion of 9.4% of patients had findings on CE that were within the reach of a gastroscope. There have been similar reports in the literature, highlighting the importance of a meticulous upper/lower endoscopic examination, particularly in the context of a patient with recurrent OGB [9, 10, 33, 34].

The tumour rate in this series is low compared to several other published series [35-37]. However, earlier studies in which the tumour rate was higher are likely to have included a selected population of patients with more severe symptoms, whereas this study included patients being investigated as part of a routine clinical practice. The prevalence rate of 3% is similar to that of 2.4% found in a recent multi centre European study of patients undergoing capsule endoscopy for various indications including OGB [38]. In fact Rondonotti et al. found an inverse correlation between the number of procedures and the frequency of tumour detection in the centres included in their study [38]. Although our cohort is small, the experience mirrors that of others in showing that tumours are the commonest cause of obscure anaemia in patients under 50 years of age [39], and are equally likely to present with overt or occult bleeding.

Conclusion

In conclusion, increasing age, anticoagulation and chronic liver disease predict a positive diagnosis with capsule endoscopy in obscure gastrointestinal bleeding. All have been directly or indirectly associated with angiodysplasia and GAVE, the commonest diagnosis in these groups of patients. Although they are often the least physically fit, and arguably at greater risk of invasive procedures, the impact on their quality of life seems likely to dictate the need to pursue a diagnosis. As with other diagnoses, tumours were equally likely to present with overt or occult bleeding, but tended to occur in a younger cohort of patients, suggesting that neither age nor nature of bleeding should be considered barriers to performing capsule endoscopy in obscure gastrointestinal bleeding.

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RS wrote the initial draft, all five authors were involved in the subsequent revisions and final draft. Mark E McAlindon is the guarantor for this manuscript.

Conflicts of interest

No funding required. No conflict of interest.

References


