Video Capsule endoscopy in patients with Iron Deficiency Anaemia: Experience at a Regional Australian Service

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Abstract

Background

Few studies have examined the diagnostic yield of video capsule endoscopy (VCE) in patients with iron deficiency anaemia (IDA). This retrospective study aims to identify the yield of VCE, distribution of VCE findings in IDA and factors predictive of positive findings among patients presenting to a gastroendoscopy practice in regional Australia.

Methods

Findings of consecutive VCE studies between March 2017 and April 2020 performed in patients with unexplained IDA and negative conventional endoscopy were included in this retrospective analysis. All endoscopies were performed and reported by a single specialist physician. Relevant clinical data including demographics, medication use, haemoglobin and ferritin levels were extracted into a standardised spreadsheet with procedural findings. A positive diagnostic yield was considered when VCE diagnosed one or more lesions that could explain the IDA. Statistical analysis was used to determine variables correlated with definite VCE findings.

Results

In total 123 procedures were included. Mean age of the patients was 67.9 years. Mean haemoglobin and ferritin levels were 93.3 g/L and 11.9ug/L, respectively. Positive findings were present in 54.5% of patients with the most frequent finding being angiodysplasia (52.2%). Haemoglobin level was the only variable associated with a positive finding. A significant number of studies had significant findings outside the small bowel (41.8%), overwhelmingly within reach of conventional upper endoscopy (89.3%).

Conclusions

VCE is a valuable diagnostic modality in patients with IDA. Low haemoglobin was associated with a positive finding on VCE in this group of patients.

1. Background

Iron deficiency anaemia is a common reason for referral to gastroenterologists, occurring in around 2–5% of men and post-menopausal women [1, 2]. For the majority of these patients, an answer is found on upper and lower endoscopy, however for 20–30% further investigations are required, often targeting the small bowel [2, 3]. Suspected small bowel bleeding (SSBB) accounts for approximately 5–10% of all patients presenting with gastrointestinal bleeding and is likely in cases of persistent or recurrent bleeding despite normal upper and lower endoscopy [4]. It may be occult or overt; occult SSBB presents as iron

deficiency anaemia with or without a positive faecal occult blood test, whilst overt SSBB presents as visible bleeding (haematemesis, melena or hematochezia) with or without IDA [4].

Since its advent in the early 2000s, video capsule endoscopy (VCE) has been increasingly utilised in Australia, as well as globally in countries with sophisticated health care systems, for the diagnosis of small bowel pathology. The success of VCE has been attributed to its high diagnostic yield, safety, and tolerability, however considerable variability in diagnostic yield exists amongst studies. In particular, there is considerable variability amongst studies that investigate IDA as the indication for VCE. A systematic review by Koulaouzidis et al. [5] reported a diagnostic yield for VCE in IDA of 66%. However, yields as low as 25% have also been reported [1]. Guidelines released by the European Society of Gastrointestinal Endoscopy (EGSE) highlight the lack of available data on predictive factors of positive VCE findings in patients with IDA [1]. Associations between increased yield and greater age, severity of anaemia, concomitant use of anti-coagulants or non-steroidal anti-inflammatory drugs (NSAID), weight loss and various comorbidities have been suggested, however these findings need to be confirmed by further studies, especially for the Australian context [6–10].

At present there are only a handful of studies which examine the diagnostic yield of VCE and predictive factors in patients with IDA [1]. The purpose of this study was to identify the yield of VCE and distribution of findings in patients with IDA in a regional setting in Australia. The secondary aims were to evaluate whether our local findings were consistent with international data and guidelines, and to identify factors which could be used to predict positive findings on VCE in IDA patients.

2. Methods

Patients and design

This study was conducted at a single-centre private gastroenterology practice in regional Australia. A retrospective review of the local VCE database was performed for consecutive procedures conducted between March 2017 and April 2020. All patients referred to the clinic had undergone conventional investigations, including at least one upper and lower endoscopy (with negative results) in the 12 months prior to VCE. Patients could be referred by physicians practicing in a range of healthcare settings (primary and secondary, public and private). Most referrals to the facility were made by general practitioners covering a geographically broad area. The majority of VCE studies were conducted in an outpatient setting, with a minority performed among in-patients.

IDA was defined using laboratory values as haemoglobin < 120 g/L for women, < 130 g/L for men and ferritin < 30 ng/L [11]. Severity of anaemia was classified according to haemoglobin levels: mild (normal – 110 g/L), moderate (< 110 g/L – 80 g/L) and severe (< 80 g/L) using cut-offs defined by the World Health Organisation in 1989 [12]. Exclusion criteria included age < 18 years, any pre-existing gastrointestinal condition believed to be the source of IDA (inflammatory bowel disease, coeliac disease, inherited polyposis syndromes), any extra-intestinal condition believed to be the source of IDA (haematological disorders, menorrhagia) or any known contraindication to VCE. All VCE studies were

reviewed by a single experienced gastroenterologist with over a decade of experience in performing and interpreting VCE studies.

The procedure reports were recorded in a local, secure database and included the following information: indication for the examination, gastric transit time, small bowel transit time, findings and conclusions.

Equipment

All VCE examinations were performed using the Pillcam SB3. The Pillcam SB3 measures 26.2 mm by 11.4 mm and weighs 3.0 g. It has a field of 156°, a battery time lasting 12 hours, and captures 2–6 frames per second. The capsule transmits the acquired data to the data recorder unit which is located outside the patient's body. Images are then transmitted from the recorder to the workstation computer for analysis. All VCE studies were analysed and reported using the Medtronic rapid reader software by the same gastroenterologist.

Procedure

All VCE examinations performed at the practice followed rigorous standards of practice and all patients provided informed written consent for the procedure. All patients were provided both verbal and written instructions prior to the procedure. Patients were instructed to cease oral iron medications three days prior to the Pillcam examination and to make the following dietary modifications 24 hours before the procedure: light, low-fibre lunch the day before, liquid-only diet the night before. Patients were required to be fasting for 6 hours before the procedure and were instructed to have two litres of water 3 hours before procedure. Following capsule ingestion, patients were required to consume nothing for three hours, after which point, they could start consuming liquids. Five hours after ingestion of the capsule, patients were able to eat and drink normally. Patients were instructed to remove the recording belt when the blue battery light stopped.

Interpretation of findings

In addition to the VCE procedure data listed previously, relevant demographic and clinical data was extracted from the VCE database and transferred to a standardised spreadsheet. The following were recorded: age, gender, NSAID use, anticoagulant use, iron replacement therapy, blood transfusion and relevant comorbidities. Most recent haemoglobin and ferritin values were also documented.

Bowel visualisation was characterised as good or poor depending on whether the mucosa was visible for evaluation. Studies with poor views were included for analysis only when significant findings were reported. A complete study was defined as the capsule passing through the ileocecal valve during its recording time of 12 hours. Incomplete studies were those in which the capsule did not reach the cecum in its working time. Capsule retention was defined as non-passage of the capsule into the cecum within 2 weeks of ingestion.

All capsule endoscopy findings were documented, and assigned a significance level (P0,1,2) using the Saurin criteria according to their relevance and likelihood of being the cause of IDA [13]. P2 lesions were considered a definite cause of IDA and only these studies were included as positive findings in the results. P2 lesions include: significant angioectasia, ulceration and widespread erosion, tumours, polyps or varices, fresh or active bleeding and significant findings outside the small bowel. Negative studies included P1 lesions of uncertain bleeding potential and P0 findings indicating normal studies.

Statistical analysis

A descriptive analysis of data was performed using IBM SPSS Statistical Software Program (Version 25). Normality tests were initially carried out to study the distribution of the variables. Continuous data was presented as mean (95% confidence interval using the t-distribution) or median (interquartile range) for normally distributed and skewed data, respectively. An unpaired student t-test (for normally distributed data) or the Wilcoxon rank sum test (for skewed data) was used for comparing the distribution of selected variables among those with positive and negative endoscopy findings. Proportional differences in outcomes were assessed using a Pearson's χ^2 test or Fisher's exact test. A p -value < 0.05 was considered as statistically significant.

3. Results

Of 297 studies performed during the specified period, 123 studies performed in 120 patients fulfilled the study inclusion criteria. In 156 patients, data were incomplete to determine their eligibility for inclusion. Two patients were excluded as they were aged < 18 years, and another 15 patients were excluded as they underwent VCE for other indications (Peutz Jeghers syndrome = 4, abdominal pain = 4, diarrhoea = 3 and carcinoid syndrome = 2) or were previously diagnosed as having coeliac disease ($n = 3$). There were three repeat procedures; one due to prolonged gastric transit and two due to poor views. The mean small bowel transit time was 4 hours and 39 minutes (range 40 minutes to 10 hours and 49 minutes) (Table 1). The completion rate, defined by visualisation of the caecum, was 92.7% (Table 1). There were no retained capsules during the study period.

Table 1
Comparison of the clinical profile and examination findings among the study population

Variables	<i>Total study population (n = 123)</i>	<i>Positive Findings (P2) (n = 67)</i>	<i>No Positive Findings (P1, P0) (n = 39)</i>	<i>p-value</i>
Mean age	67.92	69.10	66.50	0.162
Male: female	49:74	30:37	19:37	0.221
Mean haemoglobin (g/L)	93.33	88.42	99.21	0.005
Mean ferritin (ug/L)	11.93	11.93	11.92	0.992
Mean Gastric Transit time (minutes)	54.53	40.37	73.21	0.137
Mean Small Bowel Transit time (minutes)	279.0	292.27	264.41	0.195
Completion rate (caecum visualised)	92.7%	93.7%	91.1%	0.730
Significant findings are given in bold				

The mean age of the patients undergoing the procedure was 67.9 years (range 34 to 90 years) (Table 1). Seventy-four patients (60.2%) were women. Twenty-nine patients had overt gastrointestinal bleeding in addition to iron deficiency anaemia (23.6%) (Table 2). Sixty-two patients (50.4%) used NSAIDs and nineteen (15.4%) had received blood transfusions (Table 2). Fifty-seven (46.3%) had received iron replacement therapy. The mean haemoglobin was 93.3 g/L (range 40 g/L to 129 g/L) (Table 1). There were thirty-six (29.3%) patients with severe anaemia, fifty-two (42.3%) with moderate anaemia and thirty-five (28.4%) with mild anaemia. The mean ferritin was 11.9 ug/L (range 2 ug/L to 30 ug/L).

Table 2. Association of demographic and clinical factors with a positive yield of video capsule endoscopy

Patient characteristics	Total	With positive findings		Without positive findings	
	n (%)	n	% (95% CI)	n	% (95% CI)
Total	123	67	54.5 (45.3–63.5)	56	45.5 (36.5–54.8)
Age					
<60 years	23 (18.7)	8	34.8 (16.4–57.3)	15	65.2 (42.7–83.6)
≥60 years	100 (81.3)	59	59.0 (48.7–68.7)	41	41.0 (31.3–51.3)
Type of bleeding					
Occult	85 (69.1)	48	56.5 (45.3–67.2)	37	43.5 (32.8–54.7)
Overt (melena)	23 (18.7)	13	56.5 (34.5–76.8)	10	43.4 (23.2–65.5)
Overt (bright)	6 (4.9)	2	33.3 (4.3–77.7)	4	66.7 (22.3–95.7)
Haemoglobin (g/L)					
Mild	35 (28.5)	16	45.7 (28.8–63.4)	19	54.3 (36.7–71.2)
Moderate	52 (42.3)	24	46.2 (32.2–60.5)	28	53.8 (39.5–67.8)
Severe	36 (29.3)	27	75 (57.8–87.9)	9	25.0 (12.1–42.2)
Ferritin (ug/L)					
>15	30 (24.4)	13	43.3 (25.5–62.6)	17	56.7 (37.4–74.5)
<15	64 (52.0)	32	50 (37.2–62.8)	32	50 (37.2–62.8)
NSAID: yes	62 (50.4)	32	51.6 (38.6–64.5)	30	48.4 (35.5–61.4)
Transfusion: yes	19 (15.4)	11	57.9 (33.5–79.8)	8	42.1 (20.3–66.5)
Iron replacement: yes	57 (46.3)	27	47.4 (33.9–61.0)	30	52.6 (39.0–66.0)
Diabetes: yes	27 (22.0)	15	55.6 (35.3–74.5)	12	44.4 (25.5–64.7)
Abbreviations: NSAID - non-steroidal anti-inflammatory drugs; CI – Confidence Interval					

4. Discussion

The objective of this retrospective study was to assess the diagnostic yield and factors associated with positive findings in patients with IDA in a regional Australian setting and to compare the results with other published data. Key performance targets identified by the European Society of Gastrointestinal Endoscopy (ESGE) for VCE include lesion detection rate (diagnostic yield) of greater than 50%, caecal visualisation in greater than 80% of studies and capsule retention in less than 2% of studies [14]. In this study the overall diagnostic yield for the indication of unexplained IDA was 54.5%. This is consistent with

findings reported internationally and achieves the standard established by the ESGE guidelines. In a systematic review reporting the diagnostic yield of VCE in patients with IDA, Koulaouzidis et al. reported a pooled diagnostic yield of 66% with study yields ranging 32.5–77.7% [5]. Other recent studies have reported lower yields [15–18]. Pooling recent studies, the 2015 ESGE clinical guidelines reported an overall diagnostic yield of VCE in IDA patients of 53% [1] which is comparable to the results of our study. The caecal visualisation rate in this study was 92.5%, exceeding the minimum standard established by the ESGE. There were no retained capsules in the study period, thus achieving the standard of less than 2% retention. The excellent safety profile of VCE in IDA patients is well established, with rates ranging from 0%-4% internationally [19].

In order of frequency, the distribution of positive finding reported in this study were angiodysplasia (35/67, 52.2%), significant findings outside the small bowel (28/67, 41.8%), ulcerations and significant erosions (17/67, 25.4%), fresh bleeding (14/67, 20.9%) and tumours or polyps (10/67, 14.9%). Angiodysplasia has been widely reported as the most common finding on VCE in Western settings for both obscure gastrointestinal bleeding (OGIB) and IDA and thus that this was the most frequent finding is unsurprising. Systematic reviews by Liao et al. (OGIB) and Koulaouzidis et al. (IDA) found detection rates for angiodysplasia were 50.0% and 45.9% respectively. Other studies in patients with IDA have reported angiodysplasia to range from 25.5%-56% [6, 10, 17, 20, 21]. In comparison to published data, the number of significant findings outside the small bowel is high in our study. In IDA patients, some authors have reported higher incidence of lesions within reach of conventional endoscopy in comparison to OGIB patients [15, 21]. A recent study by Yung et al. [22] found 42% of positive studies had significant lesions within reach of standard upper and lower endoscopy thus considered “missed” findings. Other studies report lower rates of lesions outside the small bowel ranging 5%-30.3% [10, 23]. Differences between study criteria used to determine a positive finding outside of the small bowel likely accounts for some of this variability. However, the role of “second look” endoscopy prior to VCE, though recommended by current guidelines, remains controversial. Interestingly in this study, most lesions detected outside the small bowel were within reach of upper endoscopy (89.3%), suggesting that this should be prioritised over colonoscopy when considering second look endoscopy.

There is a general paucity of studies reporting factors that predict diagnostic yield of VCE in patients with IDA. Olano et. al recently reported male gender, age and haemoglobin levels as having an independent effect on the probability of obtaining positive findings [10]. Older age and severity of anaemia have also been identified by several other studies as being associated with increased diagnostic yield [6, 17]. Concomitant anticoagulant and antiplatelet therapy, increased small-bowel transit time, inpatient VCE study, history of overt bleeding and various comorbidities have also been suggested as possible positive associations with diagnostic yield, however further studies are needed to substantiate these associations [7, 18, 24]. This study demonstrated a significant association between mean haemoglobin and positive findings on VCE, which is consistent with the literature. It is likely that lower haemoglobin is an indicator of greater or more persistent blood loss over time and thus of lesions detectable on VCE. Though this study did not find a statistically significant association between age or gender and increased diagnostic yield, there was a trend for positive findings in both these groups. No other clinical or demographic

factors analysed in this study were found to predict yield. Surprisingly, anticoagulant therapy, NSAID use and overt bleeding were also not predictors of positive results. Future studies should focus on these parameters to further identify patient's most likely to benefit from VCE.

Like many studies published in the field, our study was retrospective and thus limited by incomplete data and a modest sample size. Due to referral patterns at the practice, follow-up and management outcomes were difficult to ascertain and as a result analysis of management strategies and treatment outcomes was not attempted in this study. It has been established that time to VCE after a bleeding event is associated with higher diagnostic yield [1] such that the ESGE identified a target of 90% of patients undergoing VCE within 14 days of an overt bleeding event as a key performance indicator [14], however this may be difficult to achieve in regional settings such as in Queensland. In this study, patients were often referred from rural and remote settings following initial work-up in regional centres. This means that delays to VCE were common. A strength of this study in relation to others published in the field is the strict inclusion of only patients with IDA. There is a lack of published data specific to patients with IDA; the majority of studies focused on OGIB/SSBB more broadly. In addition, there have been few, if any, VCE studies reported from a regional Australian setting.

5. Conclusion

This study suggests that the diagnostic yield of patients with IDA in a regional Australian practice is comparable to internationally reported data. It demonstrates that VCE is a useful investigative option in patients with IDA in whom prior investigations have failed to uncover a diagnosis. In addition, it suggests that patients with severe anaemia, as reflected by haemoglobin level, are more likely to have positive findings on VCE and should be referred as a priority by practitioners. Older male patients may also be more likely to have positive findings on VCE though this was not proven in our study. The high proportion of findings within reach of conventional endoscopy also suggests that in some patients with IDA, second-look endoscopy may be of value prior to VCE. In particular, the results of this study suggest that upper endoscopy should be prioritised in the first instance. Though more work remains to be done to clearly identify patients who would most benefit from VCE, encouragingly in those patients who do undergo the procedure over half receive a diagnosis.

Abbreviations

EGSE- European Society of Gastrointestinal Endoscopy

GAVE- gastric antral vascular ectasia

IDA- Iron deficiency anaemia

NSAID- Non-steroidal anti-inflammatory drugs

OGIB- Obscure gastrointestinal bleeding

SSBB- Suspected small bowel bleeding

VCE- Video capsule endoscopy

Declarations

Ethics approval:

Consistent with the standards and principles of the Australian National Statement on Ethical Conduct in Human Research (2007), the Griffith University Human Research Ethics Committee determined that this project did not require ethical review and approval. The decision was made on the 06/11/2020 and was effective from that date.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

None.

Funding:

None.

Author's contributions

MF is the corresponding author of this study. MF worked with RN and JP in the planning of this study. MF was responsible for data collection and compiled the excel spreadsheet for statistical analysis. MF was the primary author of the final manuscript and submitted the study for review.

RN is a specialist gastroenterologist in Toowoomba, Queensland. RN assisted with planning the study and was the reporting specialist for all VCE procedures. RN assisted with revision and drafting of the final manuscript.

JP is Senior Research Fellow with Rural Medical Education Association. JP assisted with planning of the study. JP also performed the statistical analyses for this project and assisted with revision and drafting of the manuscript.

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