Can haematological indices predict positive findings at endoscopy in anaemic patients?

AMP SCHIZAS¹, R REID², ML GEORGE²

¹Department of General Surgery, South East Thames, Queen Elizabeth the Queen Mother Hospital, Margate, UK

²Department of Colorectal Surgery, St Thomas's Hospital, London, UK

ABSTRACT

INTRODUCTION Patients with anaemia are commonly referred for bidirectional endoscopy. The aim of this study was to determine if any haematological parameters could predict positive findings at endoscopy.

PATIENTS AND METHODS A total of 209 patients had bidirectional endoscopies performed for anaemia between September 2002 and March 2004. The endoscopy reports, histology and full blood count results (haemoglobin [Hb], red blood cells [RBCs], packed cell volume [PCV], mean cell volume [MCV] and mean cell haemoglobin [MCH]) were then reviewed. Statistical analysis was performed using non-parametric tests.

RESULTS Overall, 197 patients had successful bidirectional endoscopies with 12 requiring completion barium enema. In 48 (23%) of these patients, a cause of anaemia was found with 15 (7.2%) carcinomas detected (2 upper GI and 13 lower GI). There was a significant difference in haemoglobin (9.2 g/dl versus 10.1 g/dl; $P = 0.0044$), RBCs ($3.56 \times 10^{12}/l$ versus $3.83 \times 10^{12}/l$; $P = 0.0325$) and PCV (0.279 l/l versus 0.31 l/l; $P = 0.0112$) between patients with positive findings at endoscopy and those with a normal investigation. Cancer patients had significantly lower haemoglobin (8.65 g/dl versus 10.1 g/dl; $P = 0.0103$), RBCs ($3.45 \times 10^{12}/l$ versus $3.83 \times 10^{12}/l$; $P = 0.0179$) and PCV (0.27 l/l versus 0.31 l/l; $P = 0.0298$) compared with patients with normal endoscopies. There was no significant difference in the other haematological parameters between those found to have positive findings and those that had normal endoscopies.

CONCLUSIONS Based on this study, the yield of bidirectional endoscopy is low, with haemoglobin and PCV being the most useful haematological indices of significant pathology. Ferritin and MCV did not predict the likelihood of finding a gastrointestinal cause for the anaemia.

KEYWORDS

Endoscopy – Colonoscopy – Gastroscopy – Anaemia

CORRESPONDENCE TO

Alexis Schizas, Department of General Surgery, Darent Valley Hospital, Dartford, UK
E: aschizas@doctors.net.uk

Patients with anaemia are commonly referred under the '2-week wait' for bidirectional endoscopy, which has placed increased demand on the endoscopy service.

The cause for iron-deficiency anaemia in men and post menopausal women is most commonly found in the gastrointestinal tract.^{1–7} Iron deficiency alone without anaemia in patients over 45 years has been shown to have an equally high yield of colonic pathology.^{8,9} However, the majority of '2-week wait' patients do not have their iron levels checked before referral or endoscopy.

The British Gastroenterology Society has issued guidelines advising that adult patients over 45 years without overt blood loss or any obvious cause of iron-deficiency anaemia should undergo upper gastrointestinal endoscopy including

duodenal biopsy, and colonoscopy or barium enema.¹⁰ These guidelines are not always followed.¹¹ The NICE guidance CG27 for suspected cancer recommends that urgent referrals for bidirectional endoscopy should be made for men with unexplained iron-deficiency anaemia and a haemoglobin of less than 11 g/dl and non-menstruating women with unexplained iron-deficiency anaemia and a haemoglobin of less than 10 g/dl. There is no recommendation in the NICE guidance for any further blood tests.

Haemoglobin is an iron-containing compound found in the red blood cells. Measuring the concentration of haemoglobin in the blood can diagnose anaemia, which is caused by a deficiency of haemoglobin. Red cell count is an estimation of the number of red blood cells (RBCs) per litre of

blood. Abnormally low numbers of red blood cells may indicate anaemia as a result of blood loss, bone marrow failure, malnutrition, iron deficiency, over-hydration, or mechanical damage to red blood cells. Packed cell volume (PCV) is a measure of the percentage of red blood cells to the total blood volume. A low haematocrit may indicate anaemia, blood loss, bone marrow failure, leukaemia, multiple myeloma, nutritional deficiency, over-hydration or rheumatoid arthritis. Mean cell volume (MCV) or mean corpuscular volume is an estimate of the volume of red blood cells. It is useful for determining the type of anaemia a person might have. A low MCV may indicate iron deficiency, chronic disease, pregnancy, anaemia due to blood cell destruction or bone marrow disorders. Mean cell haemoglobin (MCH) also known as mean corpuscular haemoglobin are further guides to the investigation of anaemia. The MCH is the haemoglobin content of the average red cell. The MCH may be low in types of anaemia where the red blood cells are abnormally small, or high in other types of anaemia where the red blood cells are enlarged (*e.g.* as a result of folic acid or vitamin B₁₂ deficiency). Iron-deficiency anaemia can be identified by measuring ferritin, a protein which stores iron and is directly proportional to the amount of iron stored in the body.

The aim of this study was to identify any haematological variable that could predict positive endoscopy findings thereby allowing higher risk patients to be prioritised and possibly reduce endoscopy requests.

Patients and Methods

Ethical approval was obtained from the Ethics Department of St Thomas's Hospital. All patients undergoing bidirectional endoscopy for anaemia alone between the period September 2002 and March 2004 were identified from the Endoscribe system and a review of the paper files of all the endoscopies performed in this time period. Using both these searches, we were confident that nearly all the patients that had bidirectional endoscopy to investigate anaemia were identified. Patients with anaemia and other gastrointestinal signs or symptoms were excluded. Anaemia was defined as a haemoglobin of less than 15 g/dl in men and less than 12 g/dl in women as recommended by the World Health Organization.

The haematology and histology results were found using the hospital computer results reporting system. Results were also obtained from the pathology paper files when necessary. These results were then reviewed and analysed using Microsoft Excel and Arcus Quickstat.

Haematological variables studied were haemoglobin (g/dl), packed cell volume (l/l), red cell count ($\times 10^{12}/l$), mean cell volume (fl) and mean cell haemoglobin (pg).

Pathological causes of anaemia were defined as upper or lower gastrointestinal carcinoma, erosive gastritis, erosive

Table 1 Causes for anaemia on bidirectional endoscopy

Upper gastrointestinal

Carcinoma	2
Peptic ulcer	5
Erosive gastritis	7
Haemorrhagic gastritis	3
Oesophagitis	1
Gastric vascular lesion	2
Varices	1

Lower gastrointestinal

Carcinoma	13
Rectal polyp over 10 mm	11
Angiodysplasia	8
Severe diverticulitis	1
Sigmoid colon vasculitis	1

oesophagitis, peptic ulcer, varices, colonic polyps over 10 mm, angiodysplasia and vasculitis.^{1,2,6,8,9}

Patients were divided into subgroups depending on the presence of a pathological lesion that would explain anaemia or not. If a patient underwent an incomplete study and subsequently had either a contrast study or further completion colonoscopy, this patient was only included once in the final analysis with the most definitive result being used.

Statistical analysis was performed using non-parametric tests with a significant *P*-value of less than 0.05 taken as significant.

Results

A total of 215 patients underwent bidirectional endoscopy for anaemia with a mean age of 67 years (range, 26–89 years). Four patients were excluded as their haematology was not available; none of these patients had malignancy at endoscopy. Of the remaining 209 (107 females, 102 males), 197 had completion bidirectional endoscopies. Twelve patients required a barium enema to complete their large bowel investigation. There were no complications recorded in any of the patients having undergone endoscopy and no patient required admission following the procedure.

Overall, 161 (77%) patients had normal bidirectional endoscopy. A cause for anaemia was found in 48 (23%) patients (26 female, 22 male) with 15 (7.2%) carcinomas detected (2 upper GI and 13 lower GI). The causes of anaemia identified are listed in Table 1. There was a solitary upper gastrointestinal cause in 7%, a solitary lower gastrointestinal cause in 13% and both upper and lower

Table 2 Median values and interquartile range of haematological variable in patients who have had bidirectional endoscopy

	No cause found (<i>n</i> = 161)	Cause identified (<i>n</i> = 48)	Cancer identified (<i>n</i> = 15)
Haemoglobin (g/dl)	10.1 (6.9–12.9)	9.2 (5.4–11.2) <i>P</i> = 0.004	8.65 (5.8–10.9) <i>P</i> = 0.01
Packed cell volume (l/l)	0.31 (0.20–0.47)	0.28 (0.17–0.39) <i>P</i> = 0.01	0.27 (0.19–0.34) <i>P</i> = 0.03
Red cell count ($\times 10^{12}/l$)	3.83 (2.03–5.76)	3.56 (1.89–5.09) <i>P</i> = 0.03	3.45 (2.53–4.64) <i>P</i> = 0.02
Mean cell volume (fl)	80 (52–124)	80 (53–108) <i>P</i> = 0.9	81.5 (53–91) <i>P</i> = 0.7
Mean cell haemoglobin (pg)	26.6 (13.3–42.9)	26.0 (15.5–36.7) <i>P</i> = 0.8	26.9 (15.5–30.3) <i>P</i> = 0.8

Mann-Whitney U-test.

gastrointestinal pathology in 3% of patients. No patients were found to have an upper and lower gastrointestinal carcinoma.

Patients with a cause for their anaemia were older than patients with normal endoscopies (median 72 years [range, 42–89 years] versus 68 years [range, 26–89 years]; *P* = 0.05), with patients diagnosed with cancer being even older 74 years (range, 52–84 years; *P* = 0.10), but not statistically significant.

Duodenal biopsies were taken from 182 (87%) patients having an upper gastrointestinal endoscopy with no patient found to have coeliac disease on histological examination.

Haematological parameters were correlated against those with pathology and those without. The median values and range of the haematological parameters are listed in Table 2.

There was a significant difference in haemoglobin, RBCs and PCV between patients with positive findings at endoscopy and those with a normal investigation. There was also a significant difference in these parameters between patients found to have cancer at endoscopy and those with normal endoscopy. There was no significant difference in the MCV and MCH between these groups of patients.

Ferritin was measured in 96 (46%) patients. Forty patients had a low ferritin and 7 of these patients had a cause for their anaemia identified. One patient with a low ferritin was found to have a colorectal cancer. The other causes were gastritis, gastric vascular lesion, two patients with colonic polyp and two patients with angiodysplasia. Of the 56 patients with anaemia and a normal ferritin, 7 patients had cause of their anaemia identified at endoscopy. Two of these patients were found to have gastrointestinal cancers. The other causes were varices, oesophagitis, gastric ulcer, colonic polyp and angiodysplasia. The median ferritin value of patients with normal endoscopy was 58.9

ng/ml compared with 59.3 ng/ml in the patients where a cause was found. There was no significant difference in the ferritin levels between the two groups (*P* = 0.97).

Sixty (28.7%) patients had a haemoglobin of over 11.0 g/dl of whom only 4 were found to have any pathology. All patients identified with a carcinoma had a haemoglobin of < 11.0 g/dl. The positive predictive value of bidirectional endoscopy performed on patients with a haemoglobin $\leq$ 11.0 g/dl was 29% compared to 7% in those that had a haemoglobin over 11.0 g/dl. The positive predictive value of detecting a carcinoma in a patient with a haemoglobin of $\leq$ 11.0 g/dl is 10% compared to 0% in those patients that had a haemoglobin over 11.0 g/dl.

Looking at the age of the patients, 35 (16.7%) patients, under the age of 50 years, had bidirectional endoscopy performed with only 4 having positive findings, none of which were found to have a carcinoma. Of the remaining 174 patients over 50 years of age, 44 (25%) were found to have positive findings including all the patients identified with a colorectal carcinoma.

Discussion

In recent years, there has been an expansion in the capacity of the endoscopy service but there has been an increase in the number of endoscopy requests. The introduction of the '2-week wait' has stretched endoscopy resources further.^{12–14} It was our aim to identify any haematological variable that could predict positive endoscopy findings, possibly allowing higher risk patients to be prioritised.

Previous studies investigating patients with iron-deficiency anaemia reported a wide variation in the percentage of patients found to have positive findings (Table 3), which are probably accounted for by difference in definitions for anaemia and potential gastrointestinal causes for anaemia. Some have included polyps of any size.¹¹ In the study by

Table 3 Previous studies on iron-deficiency anaemia

	Subjects (n)	Source of bleeding (%)			
		Lower	Upper	None found	Cancer
Patterson & Johnston (2003) ¹¹	95	14	21	66	10
Kepczyk <i>et al.</i> (1995) ²	70	30	56	29	10
Hardwick & Armstrong (1997) ⁴	89	56	57	16	51
Gordon <i>et al.</i> (1994) ⁶	170	18	41	41	9
Rockey & Cello (1993) ¹	100	25	36	38	12
McIntyre & Long (1993) ⁵	111	16	39	11	16

Kepczyk *et al.*,² the potential lesions considered to cause anaemia were similar to our study; however, in their study, patients were excluded if they had undergone previous investigation for iron-deficiency anaemia, were in renal failure, had previous gastric surgery or were premenopausal women.

Hardwick and Armstrong⁴ had a much higher cancer pick up rate and positive endoscopy than the other studies. Their study only included patients referred to consultant surgeons with iron-deficiency anaemia, but the cancer detection rate of more than 50% is at variance with other studies. McIntyre and Long⁵ studied patients referred by family practitioners to gastroenterology out-patients. Their study also included patients with gastrointestinal symptoms and signs on examination and they used a combination of investigations to identify the cause of iron-deficiency anaemia.

Our study looked at patients referred with anaemia that had bidirectional endoscopy only and no other abdominal symptoms or signs. Many of these patients are referred without having had iron studies performed, making them an unselected group, which reflects the referral practise at our hospital. Previous studies looking at iron-deficiency anaemia have reported cancers in 10% of patients; our study had a similar, but lower, incidence of cancer (7.2%) which reflects the unselected patient population. Interestingly, the use of surrogate markers of iron-deficiency anaemia, such as MCV, MCH and ferritin levels, did not predict positive findings at endoscopy.

Positive findings were found in only 23% of all patients and only 7% in the patients with a haemoglobin > 11.0 g/dl. Nearly one-third of patients having bidirectional endoscopy to find the cause of their anaemia had a haemoglobin of > 11.0 g/dl.

The incidence of both upper and lower gastrointestinal cancer increases with age. Bidirectional endoscopy per-

formed on patients under the age of 50 years revealed positive findings in only 4 patients (positive predictive value 11.4%), none of whom were found to have a carcinoma. This compares with the 25% positive predictive value of endoscopy for anaemic patients over 50 years of age.

Conclusions

The pathological yield in anaemic patients investigated with bidirectional endoscopy is low. The NICE and British Society of Gastroenterology guidelines advise investigation for iron-deficiency anaemia but we found that a low ferritin and MCV did not predict positive findings. Our study suggests that patients with haemoglobin lower than 11 g/dl have a higher positive predictive value. This supports the NICE guidelines for investigating unexplained anaemia when the haemoglobin is less than 11 g/dl but would suggest that less emphasis is placed on iron deficiency. Our cancer network does not request a ferritin level before referral but we are aware that others do. We would suggest, from this study, that a ferritin level is not necessary as it does not predict positive findings at endoscopy. Of greater importance would be more information on patient symptoms and confirmation of the anaemia and haematological indices in the referral. A referral proforma that asks the correct questions and insists that they are appropriately answered would help reduce inappropriate referrals.

The 2-week referral system should not be used as a depository by GPs for all cases of anaemia. After all, it was a scheme devised for the early assessment of patients in whom gastrointestinal cancer is suspected. In those cases of confirmed iron-deficiency anaemia, referral by this means also gives an opportunity for the prompt diagnosis of benign gastrointestinal disease.

References

1. Rockey DC, Cello JP. Evaluation of gastrointestinal tract in patients with iron deficiency anaemia. *N Engl J Med* 1993; **329**: 1691–5.
2. Kepczyk MT, Shailesh C, Kadakia M. Prospective evaluation of gastrointestinal tract in patients with iron deficiency anemia. *Dig Dis Sci* 1995; **40**: 1283–9.
3. Rex DK. Colonoscopy: A review of its yield for cancers and adenomas by indication. *Am J Gastroenterol* 1995; **90**: 353–65.
4. Hardwick RH, Armstrong CP. Synchronous upper and lower gastrointestinal endoscopy is an effective method of investigating iron-deficiency anaemia. *Br J Surg* 1997; **84**: 1725–8.
5. McIntyre AS, Long RG. Prospective survey of investigations in outpatients referred with iron deficiency anaemia. *Gut* 1993; **34**: 1102–7.
6. Gordon SR, Smith RE, Power GC. The role of endoscopy in the evaluation of iron deficiency anaemia in patients over the age of 50. *Am J Gastroenterol* 1994; **89**: 1963–7.
7. Moses PL, Smith RE. Endoscopic evaluation of iron deficiency anemia. *Postgrad Med J* 1995; **98**: 213–26.
8. Brooklyn TN, DiMambro AJ, Haslam N. Patients over 45 years with iron deficiency require investigation. *Eur J Gastroenterol Hepatol* 2003; **15**: 535–8.
9. Joosten E, Ghesquiere B, Linthoudt H, Krekelberghs F, Dejaegar E, Boonen S *et al*. Upper and lower gastrointestinal evaluation of elderly inpatients who are iron deficient. *Am J Med* 1999; **107**: 24–9.
10. Goddrard AF, McIntyre AS, Scott BB, for the British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. *Gut* 2000; **46**: IV1–5.
11. Patterson RN, Johnston SD. Iron deficiency anaemia: are British Society of Gastroenterology guidelines being adhered to? *Postgrad Med J* 2003; **79**: 226–8.
12. Baron TH, Kimery BD, Sorbi D, Gorkis LC, Leighton JA, Fleischer DE. Strategies to address increased demand for colonoscopy: guidelines in an open endoscopy practice. *Clin Gastroenterol Hepatol* 2004; **2**: 178–82.
13. Zamir S, Rex DK. An initial investigation of efficiency in endoscopy delivery. *Am J Gastroenterol* 2002; **97**: 1968–72.
14. Melleney EMA, Willoughby CP. Audit of a nurse endoscopist based one stop dyspepsia clinic. *Postgrad Med J* 2002; **78**: 161–4.