

ROLE OF FAECAL OCCULT BLOODS IN THE DIAGNOSIS OF IRON DEFICIENCY ANAEMIA

SHORT TITLE: FOBs in the diagnosis of IDA

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Abstract

Objective To determine whether faecal occult blood (FOB) testing in patients with iron deficiency anaemia (IDA) can predict the presence of gastrointestinal cancer.

Design Cohort study

Settings Single secondary care hospital United Kingdom

Patients All individuals aged 20 and older referred for the investigation for IDA.

Interventions Data was collected from all the patients regarding Haemoglobin (Hb), Mean Corpuscular Volume (MCV), Age, Sex, Symptomatology and medication. All patients had FOB's tests using Lab Guaiac and Haemocell methods, and then underwent gastroscopy & Colonoscopy.

Main outcome measures Accuracy, sensitivity and specificity of FOBs for identifying cancer in the upper or lower gastrointestinal tract

Results In total 292 patients completed the study. 37 patients were diagnosed with carcinoma (Colon 34, Gastrooesophageal 3). Using an optimal combination of lab guaiac and haemocell test resulted in just one colorectal cancer being missed, a sensitivity of 97%, specificity of 49% and negative predictive value of 99%. The test was less effective for upper gastrointestinal cancer, with 2/3 of tumours missed by the tests.

Conclusions Patients who have negative FOB tests are very unlikely to have a colorectal cancer and the benefits to further colonic investigation is limited. This should be carefully considered in patients with significant comorbidities, where the risks of investigation may outweigh the benefits.

Word Count: 2279

Key Words: FOB, faecal occult bloods, anaemia, iron deficiency

Introduction

Iron deficiency anaemia is the most common cause of anaemia in the United Kingdom. [1] Estimates suggest that 3-5% of men and postmenopausal women have Iron deficiency anaemia (IDA) with the level rising to 7% in elderly hospital in-patients. [2,3,4] The principal concern in patients presenting with an iron deficiency anaemia is that it may be the result of blood loss from an underlying gastrointestinal neoplasm. Previous studies have shown a prevalence of carcinoma of 10-20%, most commonly of the colon [5,6,7,8,9] (5%- 12.5%), but also stomach and oesophagus. Currently both the British Society of Gastroenterology (BSG) [10] and American Gastroenterology association (AGA) [11] guidelines recommend that upper and lower gastrointestinal endoscopy be performed in all men and postmenopausal women with iron deficiency anaemia. It should be recognised that the risk of cancer is not uniform across all age groups and gender. However, investigation is not risk free, and the complications associated with endoscopy can be more pronounced in frail, elderly patients [12], or in patients of any age with significant co-morbidities, including advanced chronic obstructive airway disease (COPD), severe congestive cardiac failure and advanced multiple sclerosis to name but a few examples. Whilst the decision to investigate healthy high risk patients is straightforward, there can be a dilemma for clinicians when faced with patients with multiple co-morbidities where the morbidity and mortality associated with further investigation is high. There is therefore a need for a simple, non invasive test to use in these groups of patients to stratify risk and predict whether invasive tests are likely to be of benefit.

There have been papers published which have demonstrate that advancing age, iron deficiency anaemia and positive faecal occult bloods are positive predictive factors for bleeding gastrointestinal lesions. [13, 14] Faecal occult blood testing (FOBs) are non invasive tests on stool samples which are examined for the presence of occult blood. Whilst results have varied between studies, FOB testing is approximately 50% sensitive for cancer in asymptomatic patients, and therefore felt to lack the sensitivity for use as a diagnostic test. [15,16,17,18,19,20,21] However, it is unclear how the presence of iron deficiency anaemia (IDA) may affect this. The development of iron deficiency in the context of a colorectal neoplasm is secondary to the tumour bleeding. It would be reasonable to question therefore whether this would improve the sensitivity of faecal occult blood testing for cancer. Until now no studies have been performed to investigate this.

The aim of this study is to determine whether Faecal occult blood (FOB) testing with iron deficiency anaemia (IDA) can predict the presence of gastrointestinal cancer.

Methods

The study has ethical approval from the Portsmouth and South East Hampshire ethics committee (LREC Reference No. 01/02/1298). Data was collected on adult patients referred for the investigation for Iron deficiency anaemia (IDA). Patients with a history of colonic polyps, inflammatory bowel disease or angiodysplasia, lynch syndrome, familial adenomatous polyposis syndrome, oesophageal, gastric or colon cancer, or a family history of bowel cancer, were excluded from the study. Information was collected from the patients regarding Haemoglobin (Hb), Mean Corpuscular Volume (MCV), Age, Sex, Symptomatology and medication. All patients

had MCV and ferritin measured. An MCV of less than 82 with a serum ferritin <12 was required for inclusion, which accounted for 90% of the recruited patients. However, it was recognized that ferritin is an indirect measure of iron stores. It is an acute phase protein and will be elevated in the presence of inflammation. Therefore in cases where ferritin was normal then serum iron, total iron binding capacity (TIBC) and transferrin was measured. If serum iron was less than 65 ug/dl, with an elevated TIBC greater than 66 umol/l and transferrin saturation of less than 15%, patients were included regardless of MCV or ferritin.

All data was prospectively collected on an electronic computer database. All patients were requested to undertake Faecal occult blood testing using the Laboratory Guaiac and Haemocell kits, used independently on 6 stool samples collected on 6 separate days. Patients were trained how to use the haemocell kit by a nurse experienced in the test, with the lab guaiac test requiring the patient to return to the laboratory for analysis 3 stool samples taken on 3 separate days. All patients then underwent gastroscopy and colonoscopy as per standard protocol. The endoscopist was blinded to the result of the FOB test. Diagnosis at endoscopy was then compared to the FOB test results. From this sensitivity, specificity and positive and negative predictive value of the FOB tests was calculated.

The guaiac faecal occult blood test method is based upon the peroxide-like activity of the haem moiety of whole or digested blood. Hydrogen peroxide in the presence of blood will liberate oxygen, which reduces phenolphthalein (colourless) to a coloured pink product. A normal person is thought to pass up to 4.5ml blood a day via the faeces. Sensitivities of the kit for detecting haemoglobin varies from 0.01mg to 6 mg Hb/g faeces. 6 mg Hb/g faeces equates to about 4ml blood/100g faeces. A positive

control was used. This was made by diluting 0.025ml of EDTA blood (with a normal Hb) in 100ml H₂O. This gives a result of '2+', which corresponds to 4 mg Hb/g faeces (2.7ml blood/100g faeces).

0+ represents no/trace of Hb/g faeces (<1.4ml blood/100g faeces).

1+ represents 2mg Hb/g faeces (1.4ml blood/100g faeces).

2+ represents 4mg Hb/g faeces (1.4ml blood/100g faeces).

3+ represents 6mg Hb/g faeces (4.1ml blood/100g faeces)

4+ represents 8mg Hb/G faeces (5.4ml blood/100g faeces) or more.

The haemocell test is based on similar principles, but is a card based test. Faeces are applied to one side of a thick piece of paper attached to a thin film coated with guaiac using an applicator. This is done by the patient at home. In the laboratory hydrogen peroxide is applied to the inner guaiac paper. This oxidises the alpha-guaiaconic acid to a blue coloured quinone. In the presence of haemoglobin this reaction is catalysed and occurs very rapidly. The test kit is reported as either 0 (negative) or 1 (positive). 3 samples are returned, taken on 3 separate days. If any of these tests turns positive the test is defined as positive. SPSS 18(IBM Ltd) was used for the statistical calculations. A Fishers exact test was used for significance testing.

Results

In total 317 patients were enrolled, with 292 patients completing the study. In total 25 patients failed to complete the study, either for not returning all of their FOB kits or by declining definitive investigation. The median age was 70 (range 21-90). 156 were male. The median Haemoglobin was 10 g/dl (range 7-14). The median MCV was 75fL (range 57.3-97.2). The median ferritin was 17ng/mL (range 2-660). **The true**

pathology found at definitive investigation is shown in table 1.

Receiver operating characteristic (ROC) curve for laboratory guaiac test

To determine the optimum cut off point ROC curves were produced. There were 37 cancer cases in the series, 3 upper gastrointestinal and 34 colon cancers. The fitted ROC area was 0.781. Using the optimum cut off point of 2+ for positive, six true positive cases (2 Upper gastrointestinal and 4 lower gastrointestinal) were missed. **There were 122 false positive cases.** This resulted in a sensitivity of 83.8% (95% C.I. 68-93%), specificity of 52.2% (95% C.I. 50-54%) and overall accuracy of 56.2% (95% C.I. 52-59%). This equates to a negative predictive value of 96% (95% C.I. 92-98%) and a positive predictive value 20% (95% C.I. 17-23%). See table 2 and figure 1.

The analysis was repeated with upper gastrointestinal cancers excluded. The fitted ROC area was 0.792. In total 4 cancers were missed. Using the optimum cut off point of 3+ a sensitivity of 88.2% (95% C.I. 73-96%), specificity of 52.3% (95% C.I. 50-53%) and overall accuracy of 56.5% (95% C.I.53-58%) is achieved. This corresponds to a negative predictive value of 97% (95% C.I. 93-99%) and a positive predictive value of 20% (95% C.I. 16-21%). See tables 3 and 4 and figure 2.

The Haemocell test

There were 3 cases where Haemocell samples were not processed. These were excluded from analysis. For Haemocell testing alone a sensitivity was $26/37=70.3\%$ and specificity of $223/252=88.5\%$ was achieved. When upper gastrointestinal cancers were excluded the sensitivity increased to $25/34=73.5\%$. The specificity was unchanged. When combined with the guaiac test (3+ positive) a sensitivity of $34/37=92\%$ and specificity of $123/252=49\%$ was achieved. When upper gastrointestinal cancers were excluded this increased to the sensitivity to $33/34=97\%$. Specificity was unchanged. This is summarised in table 5.

Cases diagnosed with Cancer

Of the 37 patients diagnosed with carcinoma, one was oesophageal, two gastric and 34 were colonic cancers. All of the upper gastrointestinal tumours were symptomatic and would have required gastroscopy on a basis of symptoms alone. Of the four colon cancers missed by lab guaiac testing alone two were symptomatic. The other two were both right sided lesions. These would not have been diagnosed by a flexible sigmoidoscopy. Both were aged over 80 years of age. One had no comorbidities, the other having a history of previous Jaundice (resolved) and hypertension.

Discussion

Faecal occult bloods have not traditionally **been** felt to be useful as a diagnostic test for gastrointestinal malignancy. However, this data suggests that in a population with

iron deficiency anaemia, a combination of the Haemocell and guaiac tests can achieve a negative predictive value of 99% for colorectal cancer. This is perhaps not surprising. For a tumour to cause an iron deficiency anaemia requires it to bleed. Therefore it is biologically plausible that in this population the sensitivity for cancer would be much better than in a surveillance population where non bleeding tumours would be missed. This has implications for frail patients where investigation with either colonoscopy or computed tomography scanning carries increased risks.

Studies have been conducted to determine the value of immunological faecal occult blood testing in high risk populations. One small study of fifty patients looked at FOBs in patients with anaemia, achieving an overall sensitivity for adenomas and cancer of 53% and specificity of 86%.[22] However, this was attempting to find benign adenomas as well as cancer, most of which do not bleed unless large. Another study has suggested that patients with iron deficiency anaemia who test positive with a faecal-immunochemical (FIT) test are more likely to have a lesion detected at endoscopy (79% vs 27% $P < 0.001$) [23]. In this study testing was performed on a single day, and this may have limited its effectiveness. We believe that testing on multiple days improves accuracy of faecal occult bloods and therefore our data is not contradictory to this. Whilst we have not used the FIT test the principle behind the test is essentially the same. There has been data published which suggests that FIT is a more effective test than the Guaiac test.[24-26] We believe that better results would be achieved if FIT testing were used in place of the Guaiac test. These were unavailable when we started this study but are now widely available, and we feel that it would be valuable to repeat this study using FIT testing to investigate this concept further.

The key strengths of our study is that it is large and based in a real world unselected population of patients with iron deficiency anaemia. We would stress that we do not see this as a replacement for the endoscopic investigation of patients with iron deficiency anaemia; this remains the gold standard investigation and for the majority of patients this is the best form of investigation. However, there is a significant group of patients with asymptomatic iron deficiency anaemia who are frail with multiple co-morbidities where colonoscopy is a high risk procedure. It is not always ideal to perform computed tomography imaging in this group when renal impairment is a factor, as intravenous contrast is nephrotoxic. Furthermore, if a pneumocolon is performed bowel preparation is still required which in a patient with limited mobility can be very challenging. With an ageing population this is an increasingly common presentation and one which poses a difficult dilemma for investigation. We feel that if a non invasive test such as the faecal guaiac and haemocell tests could be used with a 99% negative predictive value it would potentially be a good option and much safer than invasive investigations which may cause more harm than they solve.

It could be argued that in patients where investigation is high risk the likelihood of successful treatment were a cancer found is very low, and the question could be asked whether any investigation in this group of patients is justified. However, diagnosis is not just about treatment. Patients need to be able to plan their lives. It is a reality of modern medical practice that we are often referred patients to investigate for potential cancer who would not be fit for curative treatment. Whilst it may be true that a diagnosis will not alter management, and observation may be a reasonable option, this often leads to unsatisfactory discussions with prolonged anxiety for

patients, the vast majority of whom will not have cancer. It is in these situations that FOB testing may have a role.

There may also be implications for this data in younger, low risk patients. In young, pre menopausal women with iron deficiency anaemia and no other risk factors the risk of colon cancer is very low. Faecal occult blood tests may be a reasonable measure in this cohort, providing an additional degree of reassurance without the risks associated with an invasive colonoscopy.

The combination of tests appears to provide the optimum detection of cancer. There are a number of potential reasons for this. The Haemocell test and lab guaiac test work along essentially the same principles. **The haemocell test in isolation missed 9 colorectal cancers. The guaiac test detected 8/9 of these missed lesions. In contrast, the guaiac test missed 4 cancers. The haemocell test detected three of these. In 23 cases there was agreement between the two tests. Therefore, whilst both tests were effective in isolation, there was additional gain when used together.** We suspect that the reason for the improvement in cancer yield is simply an increase in the number of samples examined. Taking the additional samples for the Haemocell test also effectively increases the period of time over which collection takes place. This may also result in an increased likelihood of detecting cancers which are intermittently bleeding. This is speculative, and warrants examination in further studies.

It should be noted that guaiac testing alone produced very good results, with an NPV of 97%. This raises a very critical question; what is an 'acceptable' cancer miss rate for a diagnostic test? There are many factors which influence this decision and it is not an easy question to answer. It is a controversial issue which this paper cannot

answer. We feel that before it can be addressed with confidence the results from this paper need to be replicated in further studies to confirm the NPV for guaiac testing both alone and in combination with the haemocell test.

There are known clinical variables which are strongly predictive for the risk of gastrointestinal cancer in iron deficiency anaemia. This includes age sex and haemoglobin. We did not find any significant difference in the age or gender of patients with cancer compared to patients without cancer in this cohort but this does not constitute an analysis of these variables and the study was not designed or powered for this purpose. We suspect that FOBs would provide additional gain in addition to these established risk factors and would be an important area for future study.

There are some limitations to our study. It is a single centre study in the United Kingdom and the population may differ elsewhere in the world. Patients were recruited across the entire adult age range, and by definition did not contain any patients unfit for either colonoscopy or CT pneumocolon. In practice it is very difficult to study a population unfit for colonoscopy, as it is not possible to establish the true diagnosis without definitive investigation. It is not simply a basis of age as many older patients are very suitable for colonoscopy and simply restricting the population to fit elderly patients would not alter this situation. We feel that the extrapolation is reasonable and probably unavoidable. It should also be noted that the number of upper gastrointestinal cancers in this series were small, and it is not possible to draw any meaningful conclusions from just 3 cases. However, given that 2/3 of the upper gastrointestinal cancers were missed, it seems probable that the guaiac FOB test is

not effective for the identification of oesophageal or gastric malignancies. This should be confirmed by larger studies, but at present could not be recommended for this purpose. Practically gastroscopy is much lower risk than colonoscopy and even very frail patients can usually tolerate a gastroscopy with very limited risk so from a clinical position this is less of an issue.

We did not perform an analysis for the sensitivity of FOBs for the detection of adenomas. There is a good volume of published literature which have demonstrated that the sensitivity of FOBs for adenoma detection is poor and we are not challenging this position. We would stress that we are not proposing FOBs as a replacement for colonoscopy. In patients where the identification of adenomas is important colonoscopy or CT pneumocolon is required. There are however patients where we simply wish to exclude cancer (i.e. patients with extensive co-morbidities and a limited life expectancy) where adenoma detection is not important. It is in these circumstances where we see FOB's as having a role.

The positive predictive value of this test is poor. There are a number of possible explanations for this. Any cause for blood in the stools can cause the FOB test to be positive, including Haemorrhoids and fissures. This is not unexpected and represents a limitation of FOBs as a technique for investigating anaemia using a non-invasive test such as FOBs. We do not propose that FOBs can be seen as a definitive diagnostic test. We feel however that they potentially have a value as a screening test with a potential value in excluding patients from further investigation who test negative.

Conclusions

Faecal occult blood testing using a combination of the guaiac and haemocell tests is a sensitive test for cancer in patients with iron deficiency anaemia. We feel negative FOB testing in patients with iron deficiency anaemia is an effective way of screening out low risk patients where further invasive investigations pose a significant risk. This data needs repeating in a similar study to establish whether this concept can become a routine aspect of clinical care.

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Statement of interests

No personal interests

No funding interests

Gastroscopy	
Normal	137
Barrett's	10
Oesophagitis	43
Hiatus hernia	73
Gastritis / gastric erosions	39
Gastric ulcer	4
Duodenal ulcer	4
Other (Polyp, GAVE)	36
Coeliac	2
Oesophageal cancer	1
Gastric cancer	2
Colonoscopy	
Normal	133
IBD	3
Angiodysplasia	5
Diverticulosis	75
Adenomatous Polyps (VA+TVA with LGD)	35
Hyperplastic	22
Cancer	34
Benign stricture	4

Table 1: Breakdown of the true diagnosis found at gastroscopy and colonoscopy

Guaiac result	0	1+	2+	3+	4+
Cancer	3	3	3	11	17
No Cancer	81	52	46	50	26

Table 2: Frequency of findings of guaiac test by pathology for all gastrointestinal cancer

Guaiac result	0	1+	2+	3+	4+
Cancer	3	1	3	11	16
No Cancer	81	52	46	50	26

Table 3: Frequency of findings of guaiac test by pathology for colorectal cancer

	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Accuracy (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)
4+ FOB	47% (32-62)	91% (89-93)	86% (82-93)	41% (28-54)	93% (91-95)
3+ FOB+ve	79% (63-91)	71% (69-73)	72% (68-75)	27% (21-30)	96% (93-98)
2+FOB +ve	88% (73-96)	52% (50-53%)	57% (53-58%)	20% (16-21)	97% (93-99)
1+ FOB+ve	91% (76-98)	31% (29-32)	38% (35-40)	15% (12-16)	96% (90-99)

Table 4; Sensitivity, specificity, Negative predictive value (NPV) and Positive predictive value (PPV) of guaiac test for the identification of colorectal cancer

	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Accuracy (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)
Haemocell alone	74% (57-86)	89% (86-90)	87% (83-90)	46% (36-54)	96% (94-98)
Haemocell with 3+ Guaic	97% (84-100)	49% (47-49)	55% (51-55)	20% (18-21)	99% (96-100)

Table 5: Accuracy, sensitivity and specificity of the Haemocell test +/- guaiac test for the diagnosis of colorectal cancer

Figure 1: ROC curve for detection of upper and lower gastrointestinal neoplasia using the faecal guaiac test (blue curve) with 95% confidence intervals (green and red curves)

Figure 2: ROC curve for diagnosis of colorectal cancer using the faecal guaiac test (blue curve) with 95% confidence intervals (green and red curves)