Extended Cr-51 RBC combined with Tc-99m RBC for the detection and localisation of occult GIT bleeding

by

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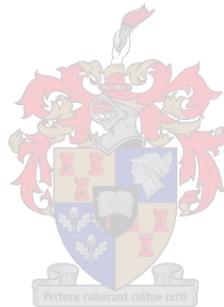
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Declaration

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Contributions

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ABSTRACT

Background

Occult blood loss from the gastrointestinal tract (GIT), causing iron deficiency often with anaemia, can be diagnostically and therapeutically challenging. This is because the endoscopic and radiologic tests may be negative due to the slow, chronic and intermittent nature of the gastrointestinal bleeding, making timing key in detection and localisation of the bleed. These limitations can be approached using two different radioactive isotopes. Firstly, we tested the sensitivity of extending Cr-51 RBC for 21 days relative to 5 days to detect GIT bleeding and its use to optimise timing of a Tc-99m RBC study for GIT blood loss localisation. Finally, we tested if the information provided by the Tc-99m RBC study aided gastroenterologic intervention for anatomical localisation of a lesion.

Method

In this retrospective review, after obtaining institutional and ethics committee approval, records of patients referred for evaluation of possible GIT blood loss were reviewed. In each; daily appearance of radiochromium in stool was measured in the whole body counter. In those cases exceeding 50 ml/day, a technetium-99m (Tc-99m) localization study was performed. These studies were correlated with clinical findings.

Results

A total of 59 Cr-51 RBC studies were carried out in 36 females and 21 males (n = 57). In 32 (54%) the radiochromium results were positive with 75% of the bleeding incidences occurring after 5 days of stool collection. Of 17 cases in whom Tc-99m

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RBC imaging studies were performed, 14 (82%) were positive with specific anatomical sites successfully defined in twelve. In all patients with blood loss of >100 ml/24h, Tc-99m RBC were positive and localised. Ten of the 17 Tc-99m RBC studies were further investigated and half diagnosed with small-bowel angiodysplasia.

Conclusion

This sequential twin isotope method is practical in revealing otherwise silent intestinal haemorrhage. Although it has good patient acceptability and clinical as well as diagnostic utility in management, further studies are required to clearly establish a cut-off level of blood loss for performing imaging studies and the impact of the findings on the overall patient management.

OPSOMMING

Agtergrond

Die evaluasie van okkulte bloedverlies uit die gastro-intestinale kanaal (GIT), met gevolglike ystertekort anemie, kan diagnosties en terapeuties uitdagend wees. Dit is omdat endoskopiese en radiologiese ondersoeke negatief mag wees as gevolg van die stadige, chroniese en intermitterende aard van die gastro-intestinale bloeding, wat die presiese tydstip van opsporing en lokalisering van die bloeding krities belangrik maak. Hierdie beperkings kan aangespreek word deur twee verskillende radioaktiewe isotope te gebruik.

Eerstens is die sensitiwiteit van die verlenging van die Cr-51 RBS studie tot 21 dae in plaas van 5 dae om die GIT bloeding op te spoor, getoets, asook die gebruik daarvan om die optimale tyd vir 'n Tc-99m RBS studie om die GIT bloedverlies te lokaliseer, vas te stel.

Laastens is getoets of die inligting van die Tc-99m RBS studie wel bygedra het tot die gastroenterologiese ingreep om die letsel anatomies te lokaliseer.

Metode

Na institusionele en etiese komitee toestemming is inligting van pasiënte wat vir die evaluering van 'n moontlike GI bloedverlies verwys is, in hierdie retrospektiewe oorsig nagegaan. Die daaglikse voorkoms van radioaktiewe chroom in stoelgangmonsters is in 'n heelliggaamteller gemeet. In gevalle waar dit 50 ml/dag oorskry het, is 'n tegnesium 99m (Tc 99m) studie gedoen. Hierdie studies is met die kliniese bevindinge gekorreleer.

Resultate

'n Totaal van 59 Cr-51 RBS studies is in 36 vroue en 21 mans (n = 57) gedoen. Die gemerkte chroomstudies was positief in 32 (54%), met 75% van die bloedings wat meer as 5 dae na versameling van die stoelgang plaasgevind het. In veertien (82%) van die 17 gevalle waar Tc-99m RBS studies gedoen is, was die studies positief. Spesifieke anatomiese gebiede van bloeding kon in 12 hiervan suksesvol bevestig word. Tc-99m RBS studies was positief in al die pasiënte met 'n bloedverlies van >100 ml/24h, en kon gelokaliseer word. Tien van die 17 Tc-99m RBS studies is verder ondersoek en die helfte daarvan gediagnoseer met dunderm angiodisplasie.

Gevolgtrekking

Die opeenvolgende twee isotoopmetode om andersins asimptomatiese dermbloeding op te spoor, is prakties uitvoerbaar. Alhoewel die studies goed deur pasiënte aanvaar is, en ook van kliniese en diagnostiese waarde in die hantering van die pasiënte is, is verdere studies nodig om die afsnypunt vir die hoeveelheid bloedverlies om beeldingstudies uit te voer, sonder twyfel vas te stel, asook om die impak van die bevindings op 'n groter pasiëntpopulasie vas te stel.

Keywords

Cr-51 labelled erythrocytes

Tc-99m labelled red cells

Gastrointestinal (GI) tract bleeding

Menstrual blood loss

Iron deficiency anaemia

Abbreviations

Abbreviation	Meaning
Cr-51	Chromium -51
CT	Computed tomography
FOT	Faecal occult blood test
GIT	Gastrointestinal tract
IDA	Iron deficiency anaemia
RBC	Red blood cell
SPECT	Single photon emission computed tomography
Tc-99m	Technetium-99m

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INTRODUCTION

Chronic blood loss, particularly from the GIT, may be difficult to demonstrate yet frequently attracts consultation because of otherwise unexplained albeit symptomatic iron deficiency anaemia (IDA)[1,2]. The identification of site of bleeding can be a challenge clinically [3].

It is recommended by the American Gastroenterological Association, the British Society of Gastroenterology (BSG) and other reports that faecal occult blood test (FOT), upper and lower endoscopy as well as barium studies be routinely used in evaluating such patients[2,4,5,6]. However, it has been shown by Lucas et al that investigation of the majority of patients with IDA is suboptimal[7].

In patients with IDA the bleeding is often silent, recurrent, or intermittent[8]. This makes timing of the investigation key in the ultimate objective of detection, localization and characterization of the bleeding to aid treatment[9]. Diagnostic imaging often consists of radiologic and endoscopic techniques[2,4]. Endoscopic investigations (gastroscopy and colonoscopy) form the primary investigative modality however it has been shown to have low sensitivity in patients with iron deficiency[10]. Radiologic techniques of barium enema, small bowel series, conventional enteroclysis and conventional computed tomography have low diagnostic yield[4,11,12]. Computed tomographic (CT) small bowel studies (enteroclysis and enterography), CT angiography and conventional angiography give substantial patient radiation exposure, are invasive and most importantly do not image for long durations which is key in identifying obscure and intermittent bleedings.[9]. The newer techniques of wireless capsule endoscopy and double-balloon enteroscopy show lots of diagnostic optimism in small bowel disease. However, in a meta-analysis it was recommended

that timing of the study was key in improving the outcome of capsule endoscopy[13]. With double balloon enteroscopy, it is impossible to visualize the whole gut in a single study, it is not widely available, is expensive and there are increased chances of pancreatitis and bowel perforation[14].

Tc-99m RBC scanning is widely used for detection of gastrointestinal blood loss. It allows active blood loss detection at rates of 0.05 - 0.10 ml/min[15,16,17]. It is non-invasive, requires no special patient preparation and can be imaged over a 24 h period, increasing the possibility of the detection of obscure and intermittent bleeding[18]. The additional use of SPECT/CT has been shown to increase precision of interpretation of scintigraphic findings, increasing diagnostic accuracy of conventional scans and correlative diagnoses. However, larger studies are needed to categorise patients with GIT bleeding that will benefit from the hybrid investigation[19,20].

It is evident that the sensitivity of detection of bleeding site by these investigative modalities depends strongly on the occurrence of active blood loss at the time of the investigation. To improve diagnostic yield it is crucial to conduct the investigation at active bleeding periods. The use of FOT for this role is flawed as it generates a high rate of false positive results, it is insensitive and non-specific[21], it depends on changing factors including fluctuating factors and metabolism of the haemoglobin which results in a false negative test[22] and gives no indication of the amount of blood loss[23]. Cr-51 RBC is the gold standard for detection and quantification of blood loss in stool and earlier studies have established its utility in documenting blood loss[23,24,25,26]. The radiation dose is also very low as very small doses are used for the study[27]. Despite these advantages, Cr-51 RBC's has not found a significant clinical

role in patient with difficult to diagnose GIT bleeding. The reason for this may in part be related to the unpleasant nature of the investigation.

The study using Cr-51 RBC for detection and quantification of blood loss is usually conducted over a 3-5 day period. These studies were not primarily targeted at silent intermittent GIT bleeding. The fact that the physical half life of Cr-51 is 28 days and only 1% of the Cr-51 elutes from the red cell per day[28], allows the detection and quantification of bleeding to be extended beyond 5 days (up to 21 days). We are not aware of any literature on this innovative method of extending the duration of the Cr-51 RBC studies to aid the timing of the Tc-99m RBC imaging studies.

The aims of our study were to evaluate whether:

1. Extended Cr-51 RBC measurements increase sensitivity for detecting and quantifying GIT bleeding;
2. Cr-51 RBC measurements can be used to optimise timing of a Tc-99m RBC localisation study (the twin isotope method);
3. The information provided by the Tc-99m RBC study can aid gastroenterologic intervention (lesion diagnosis and treatment).

We report a retrospective analysis evaluating the usefulness of this investigative algorithm in our study population.

METHODS

Patients

The records from all consecutive cases (n=57) referred to the Nuclear Medicine Department of Tygerberg Hospital with chronic iron deficiency anaemia for Cr-51 RBC studies from January 2002 to December 2009 were retrospectively reviewed after Institutional Health Research Committee approval. These patients had negative initial GIT endoscopies and barium studies. In each case the indication was confirmed and the procedure performed according to internationally accepted guidelines including compliance with radiation safety.

Case notes analyses

Patient case-notes were analysed for demographic information, confirmation of the indications, results of previous investigations, and results of the extended Cr-51 RBC study and the Tc-99m RBC study results if performed. These data were entered into a spreadsheet so that the trend of blood loss, and when imaging studies were ordered, could be evaluated. In addition, the diagnoses at the repeat endoscopic investigation were also documented.

Cr-51 RBC labelling and faecal quantitation

After radiochromation according to the method described by Mollison[29], the labelled blood was injected and a standard retained. During the period of study all stools were collected in 1 liter containers. These were brought to the nuclear medicine department on alternate days. Stool samples were counted in a whole body counter together with a standard and 5 ml anticoagulated blood samples which were

collected on alternate days. The standard is used for quality control purposes to monitor the count variations in the whole body counter (which is mostly negligible). Blood loss was calculated according to the following formula:

Blood loss in ml=Total count per minute of stool sample/counts per minute per ml of blood[30] (background corrected).

According to O'Neill et al blood loss >3 ml/day was regarded as abnormal[31].

The technique described by Ebaugh FG et al for collection and preparation of stool samples and standard consisted of stool collection over a period of 4 days[30]. We modified this technique by collecting stool samples over a longer period up to 21 days.

Technetium-99m labelled RBC imaging

In those individuals losing more than 50 ml blood per day this study was performed within 24 h, by labelling erythrocytes in vitro using Tc-99m and an UltraTag® RBC kit. Patients were scanned according to the Society of Nuclear Medicine (SNM) procedure guideline for gastrointestinal bleeding scintigraphy (version 1.0, approved February 1999). In a few cases, imaging studies were also performed when less than 50 ml blood loss has been detected based on the decision of the responsible nuclear medicine physician at that time. These included three studies (blood loss 45 ml, 48 ml and 49 ml) in which decision to image was purely based on clinical grounds

In one patient, there was also a clinical suspicion that excessive menstrual blood loss could be the cause of iron deficiency. During the study period the menstrual

volume was also determined by collecting and counting the sanitary pads. Actual loss was calculated using the same formula as for the stool.

Clinical follow-up and correlation

Based on the results of the RBC imaging, independent gastroenterologists performed endoscopic procedures to examine the localised site of bleeding and interpreted the findings in conjunction with clinical data.

RESULTS

A total of 59 radiochromium studies were carried out in 57 patients, 21 males and 36 females, age range 1.5 yrs to 81 yrs with a mean age of 50 yrs (Table 1). In one patient, three studies were done over a two year period. Menstrual blood loss of 76 ml was calculated in one patient over a menstrual period of 4 days.

Table 1: List of patients with the results of the Cr-51 and Tc-99m RBC studies

Patient number	Age (years)	Gender	Radiochromium blood loss		Technetium-99m result
			Result	Highest volume (ml/24h)	
1	67	M	negative	1.4	not done
2	66	M	positive	8	not done
3	72	M	positive	59	not done
4	65	M	positive	96.7	negative
5	72	M	positive	20	not done
6	25	M	negative	0.8	not done
7	69	M	positive	756	positive
8	37	F	positive	10.7	not done
9	75	M	negative	1.5	not done
10	64	M	negative	1.4	not done
11	73	F	positive	212	positive
12	23	F	negative	2	not done
13	3	M	negative	3	not done
14	15/12	F	negative	3	not done
15	36	F	positive	504	positive

16	60	F	positive	88	positive
17	74	F	positive	59	not done
18	33	F	negative	0.6	not done
19	52	F	negative	0.3	not done
20a	47	M	positive	14	not done
20b	47	M	positive	48	positive
20c	47	M	positive	83	positive
21	52	F	positive	45	not done
22	59	F	positive	50	positive
23	81	M	positive	145	positive
24	54	F	negative	1.1	not done
25	70	M	positive	49	Negative
26	7	M	Positive	7.4	not done
27	66	F	negative	2.2	not done
28	47	F	positive	118	not done
29	70	F	positive	5.1	not done
30	47	F	positive	6.5	not done
31	72	F	positive	38.4	not done
32	77	F	positive	239	Positive
33	49	F	negative	1	not done
34	69	F	positive	66.7	Negative
35	16	F	negative	1	not done
36	11	M	negative	0.01	not done
37	34	F	negative	1	not done
38	50	M	positive	60	positive
39	41	M	positive	3.6	not done

40	68	M	positive	84	positive
41	46	M	positive	5.1	not done
42	25	F	negative	1.2	not done
43	58	F	positive	150	positive
44	15	M	negative	0.4	not done
45	67	M	positive	5.3	not done
46	48	F	negative	1	not done
47	51	F	negative	2	not done
48	19	F	negative	1	not done
49	77	F	positive	45	positive
50	19	F	negative	1.6	not done
51	35	F	negative	1	not done
52	71	F	negative	2	not done
53	48	F	negative	2	not done
54	79	F	negative	2	not done
55	31	F	negative	2	not done
56	34	F	negative	2	not done
57	77	F	positive	193	positive

The Cr-51 RBC results were positive in 32 (54%) patients including all the examinations in the individual undergoing the 3 studies (table 2). The volume of blood loss ranged from 5.1 ml to 756 ml.

Table 2: Summary of demographics and results of radionuclide studies

| Study	Age (years)		Sex		Result		
	Range	Mean	F	M	Positive	Negative	Total
Cr-51 RBC	1.5-81	50	36	21	32 (54%)	27 (46%)	59
Tc-99m RBC	36 -81	65	9	8	14 (80%)	3 (20%)	17

The result of the extended Cr-51 RBC (table 3 and fig 1) shows the majority (75%) of the positive Cr-51 RBC occurred after 5 days.

Table 3: Extended Cr-51 RBC results

Cr-51 RBC	3-50 ml/24h		>50 ml/24h	
Day of Positivity	≤5 days	>5 days	≤5 days	>5 days
Number	2	14	6	10

When a binomial exact test is used to statistically compare the proportion of positive Cr-51 RBC at 5 days (8/59) and at 21 days (32/59), the p value is <0.001 This is very significant and demonstrates that extending the Cr-51 RBC to 21 days enhances detection of GIT bleed.

Fig 1: Shows number of patients in whom bleeding was detected in ≤5 days and >5 days after commencement of Cr-51 RBC study.
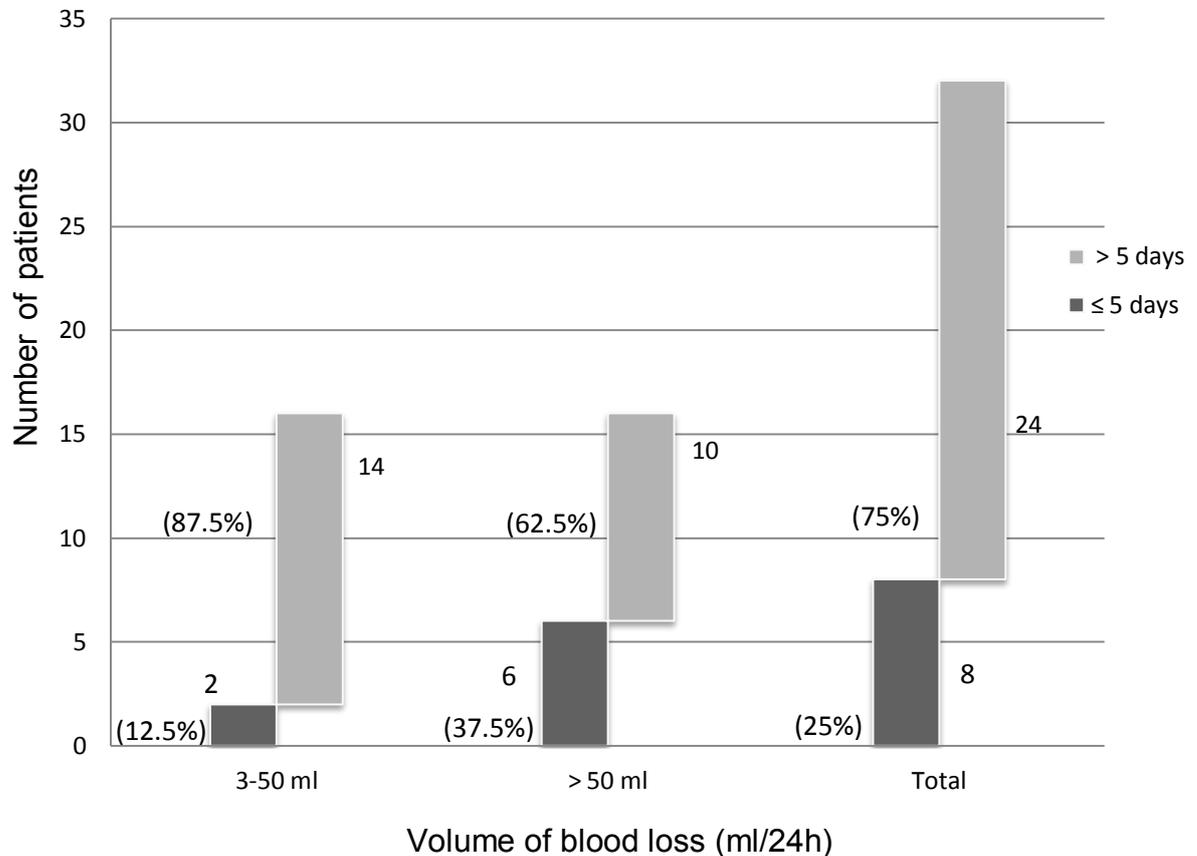
Three patients with Cr-51 blood loss greater than 50 ml were not imaged. Two had initial levels of 59 ml adjudged to be border line and subsequent measurements were below 50 ml. One lost 118 ml on one occasion. However, these could not be confirmed and the study was then not conducted.

Tc-99m labeled RBC imaging followed in 17 of the 32 positive radiochromium studies. Three of these 17 patients had Cr-51 RBC results of less than 50 ml (45 ml, 48 ml and 49 ml) and were classified in the 3-50 ml group. The decision to image was made on clinical grounds. There were 14 (82%) positive Tc-99m RBC studies (table 4), two of which were conducted at less than 50 ml (45 ml and 48ml).

Table 4: List of patients' imaging results and scintigraphic anatomical localisation

Study Code	Age (years)	Sex	Tc-99m RBC Result	Site of bleeding
4	65	M	negative	negative
7	69	M	positive	hepatic flexure (ascending colon)
11	73	F	positive	midline (small bowel)
15	36	F	positive	midline (small bowel)
16	60	F	positive	midline (difficult to localise)
20b	47	M	positive	midline (small bowel)
20c	47	M	positive	midline (small bowel)
22	59	F	positive	right iliac fossa
23	81	M	positive	right lumbar (ascending colon)
25	70	M	negative	negative
32	77	F	positive	central (small bowel)
34	69	F	negative	negative
38	50	M	positive	midline (small bowel)
40	68	M	positive	left side of midline (small bowel)
43	58	F	positive	left iliac fossa (small bowel)
49	77	F	positive	difficult to localise
57	77	F	positive	right lower quadrant (caecum, ascending colon)

The site of bleeding was localized in 11 of the 12 positive studies in the >50 ml/24h group and in the 3-50 ml/24h group 1 was localized (table 5).

Table 5: Summary of Cr-51 RBC and Tc-99m RBC results with the number of Tc-99m RBC studies that were accurately localised

Blood loss(ml/24h)	<3 (Negative)	3 – 50	>50
Cr -51 RBC	27 (46%)	16 (27%)	16 (27%)
Tc-99m RBC	Not Performed	Performed in 3	Performed in 14
Tc-99m RBC pos	-	2	12
Tc-99m RBC neg	-	1	2
Bleeding site localised	-	1	11

pos = positive; neg = negative

Classifying the 17 Tc-99m RBC studies into two groups of <100 ml/24h and >100 ml/24h led to an important finding. In all studies performed at >100 ml/24h, the Tc-99m RBC studies were positive (100%) and localized (100%). However, in the <100 ml/24h group, it was positive in 7 (70%) and localized in 5 (50%) of the studies (table 6). Using the Fishers exact test for unpaired proportions (5/10 and 7/7) the p value is 0.044. This is significant and shows that in our patient population at Cr-51 RBC blood loss of >100 ml/24h there is a 100% likelihood of Tc-99m RBC positivity and localization.

Table 6 Summary of the seventeen Tc-99m RBC studies performed and classified into two groups of <100 ml/24h and > 100 ml/24h

Blood loss (ml/24h)	<100	>100
Total number of studies	10	7
Tc-99m RBC study Positive	7 (70%)	7 (100%)
Bleeding site localized	5 (50%)	7 (100%)

Ten of the fourteen positive cases were evaluable while three were lost to follow-up and one died before further investigations could be done. In 50% the cause was a vascular anomaly. Specifically, in four there were angiodysplasia in the small intestine and in one in the gastric antrum. In the remaining five, colorectal carcinoma, benign jejunal tumor and hiatal hernia were each diagnosed once with diverticular disease occurring twice (Table 7 and figure 2).

Table 7: Clinical follow up of evaluable patients who had positive Tc-99m RBC studies

Study Code	Age (years)	Sex	Tc-99m RBC Result	Diagnosis
7	69	M	Positive	lost to follow up
11	73	F	Positive	gastric antral (Angiodysplasia)
15	36	F	Positive	hiatus hernia
16	60	F	Positive	lost to follow up
20	47	M	Positive	avm/angiodysplasia of the jejunum
22	59	F	Positive	diverticulosis
23	81	M	Positive	died before diagnosis could be made
32	77	F	Positive	benign jejunal tumor
38	50	M	Positive	colorectal carcinoma
40	68	M	Positive	angiodysplasia of the duodenum
43	58	F	Positive	ileoceacal angiodysplasia
49	77	F	Positive	angiodysplasia
57	77	F	Positive	diverticular disease

Fig 2: Shows the disease diagnoses after Tc-99m RBC study directed repeat endoscopy. Half of the evaluable cases were due to angiodysplasia.
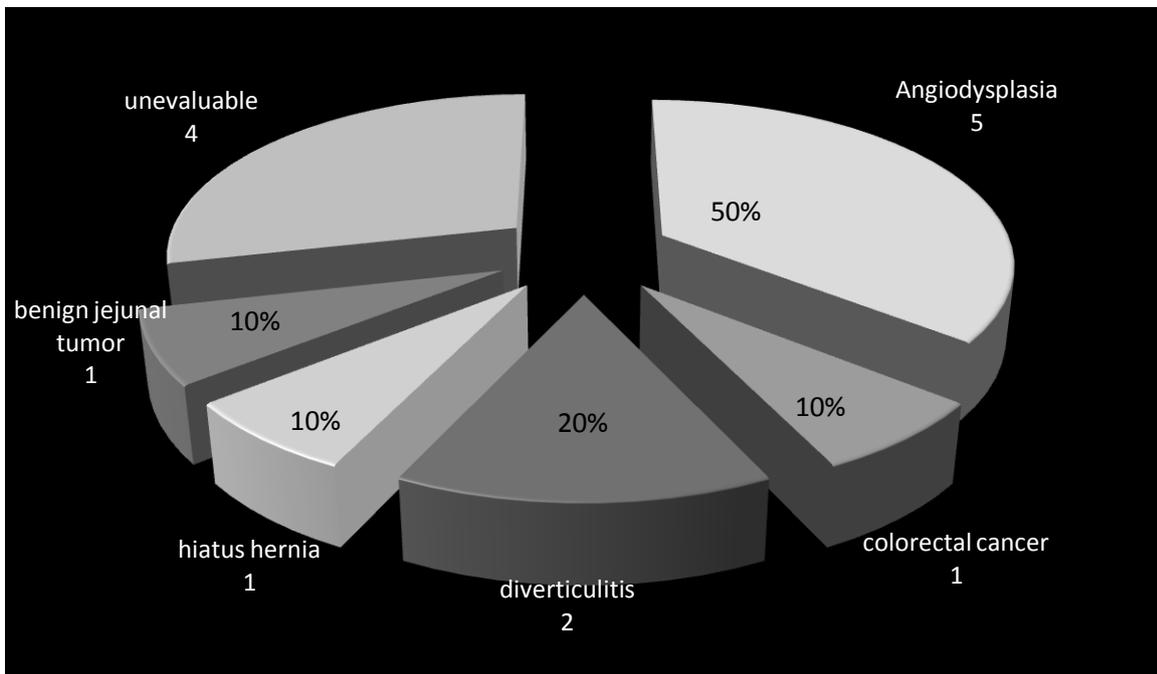
DISCUSSION

In men and postmenopausal women, GIT bleeding is considered to be the cause of iron deficiency anemia until proven otherwise[32]. When clinically evident, prompt treatment is generally effective. However, in many this may be occult and intermittent making it difficult to identify, localize and quantify.

Blood leaking into the bowel lumen varies [11,12,13,14] but up to 3 ml/day is accepted as physiological or normal[14]. In our series 32 (54%) of those tested exceeded this limit.

The extended Cr-51 RBC study (>5 days) picked up 75% of the patients with detected GIT bleeding. This finding is not strange as GIT bleeding is often intermittent. Extending the duration of the investigation resulted in increase in the ability of the test to detect the presence of bleeding in the GIT.

As this extended and two phased approach has not yet been described, we decided to empirically use 50 ml blood loss on the radiochromium study as cut off to do imaging studies. There were 14 (82%) positive Tc-99m RBC studies, two of which were conducted at less than 50 ml (45 ml and 48ml) and we clearly localized the site of the bleeding in 12 (86%) of the 14 cases. This high detection rate indicated that the chosen level of stool positivity (50 ml) was a realistic value. However, the validity of this selection will need further confirmation as we also detected positivity at less than 50 ml in 2 of 3 patients. A well structured prospective study that includes all positive Cr-51 RBC studies will help confirm the existence of a cut-off blood loss level.

A potential value of quantifying Cr-51 RBC in stool is to schedule imaging investigations when there is evidence of bleeding, to aid localization of bleeding sites

in the GI tract enabling better definition of the pathologic lesion. We are not aware of any reports advocating this method to initiate localization studies and to set a level of 50 ml as realistic in specifying significant haemorrhage. Our study showed that at GIT blood loss of >100 ml/24h, there is a 100% detection rate and site of bleeding localization rate. However, the sample size is small and further verification is required.

Tc-99m RBC studies directed repeat endoscopic evaluation of the GIT and aided the identification of the cause of bleeding in the majority of our patients. In evaluable patients, vascular anomalies accounted for 50% of the active lesions identified, the majority of which were located in the duodenum or jejunum. Angiodysplasia can occur at any level in bowel and be clinically silent or present as occult blood loss[33]. Incidence increases with advancing age to become common in those over 60 yrs[33] accounting for 30-40% of cases[34]. The average age of our patients with this proven diagnosis was 62.5 yrs.

Although this pathology is the most fequent[34], it does need to be distinguished from other causes including colorectal carcinoma as there are major differences in management[32,35].

In premenopausal women, menstrual blood loss is the commonest reason for iron deficiency[34] and the contribution from bowel is variable[36]. Provided the investigation is properly structured a single radiochromium study can reliably separate the two causes[37]. In our patient 76 ml of blood loss was measured over a four day period, which is below the 80 ml accepted cut-off level for menorrhagia[38].

The retrospective nature of this study influenced adequate retrieval of patient clinical information. Information concerning the treatment of identified cause of bleeding, and whether this resulted in subsequent cessation of the bleeding and normalisation of the iron deficiency was unobtainable. In addition, this study is limited as stools were not counted every day which could result in missed opportunities for imaging. The study is also labour intensive and time consuming for the patients due to frequent hospital visits. However, in cases of difficulty in diagnosis and localisation of a GIT bleeding site in a patient with iron deficiency it may avoid unnecessary invasive procedures.

CONCLUSION

This sequential twin isotope method is a practical way to approach otherwise silent bleeding from the bowel. Extension of the Cr-51 RBC study for more than 5 days increased GIT bleeding detection rate. Further studies are required to clearly establish a cut-off level and the impact of the findings on the overall patient management. However, the study is well accepted by patients, can avoid unnecessary diagnostic procedures and have clinical as well as diagnostic utility in management of chronic iron deficiency anaemia.

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