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Capsule enteroscopy versus radionuclide scintigraphy for the diagnosis of obscure gastrointestinal bleeding

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Authors contributions
Miguel Mascarenhas Saraiva: data collection and analysis, drafting and revision of the manuscript;
Tiago Ribeiro: data collection and analysis, drafting and revision of the manuscript;
Patrícia Andrade: critical revision of the manuscript;
Hélder Cardoso: study design, data analysis and critical revision of the manuscript;
Guilherme Macedo: critical revision and final approval of the manuscript.

Keywords: Capsule Endoscopy. Scintigraphy. Gastrointestinal hemorrhage. Iron-deficiency anemia.

List of abbreviations:
CE – capsule enteroscopy;
\textsuperscript{99m}Tc RBC scintigraphy – \textsuperscript{99m}Technetium red blood cell scintigraphy;
OGIB – obscure gastrointestinal bleeding;
DBE - double-balloon enteroscopy;
CT – computerized tomography
Conflicts of interest: nothing to disclose.

Abstract

Background: Capsule enteroscopy (CE) and $^{99m}$Tc Red blood cell (RBC) scintigraphy are frequently used tests in the investigation of obscure gastrointestinal bleeding (OGIB). There is a scarcity of data comparing both diagnostic modalities. This study aims to assess the performance of CE and scintigraphy for the diagnosis of OGIB.

Methods: Patients who underwent CE and scintigraphy for OGIB were selected and analyzed retrospectively. The hemorrhagic potential of CE findings was rated using Saurin's classification. The concordance between both diagnostic techniques for bleeding detection and localization was analyzed.

Results: Eighty-five patients (62% female), with a median age of 63 years, were included. Capsule enteroscopy identified 37 patients (43%) with high hemorrhagic potential (P2) lesions. Most scintigraphy exams were positive for gastrointestinal bleeding (82%). No concordance was found between the detection of lesions with hemorrhagic potential in CE and scintigraphy (kappa <0). The distribution of P0, P1 and P2 findings was similar in patients with positive or negative scintigraphy (p=0.526). There was no agreement regarding the location of P2 findings in CE and the bleeding detected in the scintigraphy (kappa <0). Patients with P2 lesions had significantly lower median levels of hemoglobin (p=0.002) at presentation. No significant difference was found in hemoglobin values between patients with positive or negative scintigraphy (p=0.058).

Conclusion: Significant diagnostic discrepancy was observed between CE and scintigraphy. The findings of CE correlated better with hemoglobin values at presentation than the scintigraphy results. Therefore, scintigraphy didn’t appear to be useful in the diagnostic workup of OGIB.
Introduction

Obscure gastrointestinal bleeding comprises cases of gastrointestinal bleeding, either overt or occult, with unremarkable conventional endoscopic study (upper endoscopy and colonoscopy). This entity accounts for 5% of all cases of gastrointestinal hemorrhage. The majority of these cases are due to small-bowel bleeding which poses both diagnostic and therapeutic challenges (1).

The advent of enteroscopy techniques allowing for complete bowel inspection, most notably CE, has revolutionized the approach to these patients. In fact, it is recommended as the first line in the study of OGIB by most clinical practice guidelines (1). Evidence suggests that CE is superior to push-enteroscopy, radiographic small-bowel studies and angiography (2-4). Also, CE performed similarly to double-balloon enteroscopy (DBE), and may further increase the yield of DBE (5, 6).

$^{99m}$Tc RBC scintigraphy is a widely used and highly sensitive method for the detection of gastrointestinal bleeding. It identifies bleeding with rates as low as 0.04 mL/min (7). However, it has been demonstrated that it correlates poorly with other diagnostic tests, such as angiography, and does not predict further diagnostic and therapeutic course (8, 9).

To this date, there are no studies correlating the findings of $^{99m}$Tc RBC scintigraphy and CE. Therefore, this study aims to assess the diagnostic performance of $^{99m}$Tc RBC scintigraphy and CE in patients with OGIB, either overt or occult.
Patients and methods

Participants
A total of 462 consecutive adult patients underwent CE for OGIB between January 2016 and December 2019, at the department of Gastroenterology of Centro Hospitalar Universitário de São João, in Portugal. All patients had previous negative upper endoscopy and colonoscopy for potential sources of bleeding. Non-digestive sources of bleeding were disclosed. Clinical data from 85 patients who also underwent $^{99}$mTc RBC scintigraphy was retrospectively analyzed. Concordance between both diagnostic techniques regarding bleeding detection and location was evaluated. Data respecting gender, age, indication for exams and hemoglobin levels was obtained. The study was approved by the ethics committee of Centro Hospitalar Universitário de São João.

Capsule enteroscopy
Patients with OGIB were submitted to CE using the PillCam SB3® system (Medtronic, Minneapolis, Minnesota, USA). Bowel preparation before CE, guidance for the initiation of oral diet and completion of the exam followed previously published guidelines (10). The hemorrhagic potential of endoscopic findings was determined through the application of Saurin’s classification: P0 – no hemorrhagic potential including visible submucosal veins, diverticula without blood, nodules; P1 – uncertain hemorrhagic potential, including red spots or small erosions; P2 – high hemorrhagic potential, such as angiomata, large ulcerations, tumors and varices (11). CE was considered positive if P2 findings or blood pooling were reported.

Scintigraphy
The $^{99}$mTc RBC scintigraphy was performed by in vivo radiolabeling of autologous RBCs with $^{99}$mTechnetium-pertechnetate. Dynamic images were obtained from the abdominal region. Image acquisition was performed up to 24h in some cases. The images were reviewed by nuclear medicine specialists. Suspected bleeding was reported if there was evidence of luminal extravasation of labelling material. Results available for review were compared with CE results to assess for concordance between both diagnostic systems.
Statistical analysis

Baseline characteristics of the patients, including age, gender, hemoglobin value and time between CE and scintigraphy were registered. Continuous variables are described through medians and respective interquartile range (IQR, 25th - 75th percentile). Categorical variables are expressed through frequencies (n) and percentages. Continuous variables were compared using Mann-Whitney or Kruskal-Wallis tests, as appropriate. Categorical variables were analyzed using Fisher’s exact test. The degree of agreement between VCE and scintigraphy findings was measured by kappa (κ) statistic. Correlations were assessed using the Spearman’s rank-order coefficient. A p < 0.05 was considered statistically significant. Data analysis was performed using Statistical Package for Social Sciences version 26 (SPSS®, IBM Corp., Armonk, New York, USA).

Results

Eighty-five patients underwent both CE and ⁹⁹mTc RBC scintigraphy for investigation of OGIB and were included for analysis. In most patients (86%), these exams were requested for the study of unexplained iron-deficient anemia (occult OGIB). Sixty-two percent of the patients were female, with a median age of 63 years (IQR 51 - 74). Scintigraphy was performed before CE in 91% of the patients. The median time between the two tests was 4 months (IQR 1.5 – 7.0). The ⁹⁹mTc RBC scintigraphy identified bleeding in 82% of patients. The overall diagnostic yield of CE was 43%. The most commonly described lesion was angiectasia (37%), followed by erosions (20%) and ulcers (12%). Descriptive statistics are summarized in table 1.

Concordance between CE and scintigraphy findings

The distribution of CE findings according to scintigraphy results is shown in table 2. The distribution of lesions with different bleeding potential (P0, P1 or P2) did not differ between those with positive (P0: 46%; P1: 11%; P2: 43%) or negative (P0: 33%; P1: 20%; P2: 47%) scintigraphy (p = 0.526). There was no concordance between the results of scintigraphy and the identification of lesions with hemorrhagic potential (κ =
-0.020). Similarly, no concordance existed between the topography of the bleeding in the scintigraphy and the location of potential bleeding lesion in CE (κ = -0.031).

As the interval between scintigraphy was highly variable, a sub-analysis was performed in order to assess the influence of this interval in the obtained results (table 3). In those for which CE and scintigraphy were performed with an interval larger than 2 months, the distribution of P0, P1 and P2 lesions did not differ between those with positive (P0: 50%; P1: 10%; P2: 40%) or negative (P0: 40%; P1: 20%; P2: 40%) scintigraphy (p = 0.670). Similar results were observed for those whose interval between CE and scintigraphy did not exceed 2 months (p = 0.772) (table 3).

**Relationship between presence of hemorrhage and hemoglobin values**

As shown in table 4, no statistically significant difference was found in hemoglobin levels at presentation between patients with positive or negative $^{99m}$Tc RBC scintigraphy (p = 0.058). In contrast, those with lesions with high bleeding potential in CE demonstrated significantly lower hemoglobin values (p = 0.002). Post-hoc analysis identified a significant difference between those with P2 lesions and patients with lesions without bleeding potential (Figure 1).

The presence of lesions with high bleeding potential was significantly correlated to lower hemoglobin levels (Spearman’s ρ - 0.381, p < 0.01), whereas such correlation was not apparent for those with positive scintigraphy (p = 0.058).

**Discussion**

Scintigraphy with radiolabeled RBCs has been used for the study of gastrointestinal bleeding for decades. In fact, it is reported as extremely sensitive, detecting bleeding with rates as low as 0.04 mL/minute (7). Also, it does not require bowel preparation and, due to its prolonged acquisition time, allows for the detection of intermittent bleeding. However, subjective interpretation of nuclear scans is possible, which may contribute to inaccuracy in the location of the bleeding site (7). Therefore, several studies have demonstrated the limited utility of $^{99m}$Tc RBC scintigraphy in directing further diagnostic and therapeutic approaches (8, 9, 12). Over the last years, several studies have evaluated the correlation between scintigraphic findings and the results
of other imaging tests, most frequently catheter angiography or computerized tomography (CT) angiography. Positive nuclear scan is a poor predictor of positive angiography (13). Correlation between these tests (positive $^{99m}$Tc RBC scintigraphy and positive angiography) has been measured to occur in 21-54% (7-9, 12, 14). This may be explained by the greater sensitivity of scintigraphy and low-rate intermittent bleeding, detected by nuclear scan but not angiography. It has been demonstrated that positive scintigraphy does not predict subsequent diagnostic or therapeutic steps, and its real impact on patient management is dubious (9). Therefore, its current role in the investigation of OGIB is questionable.

Capsule enteroscopy has revolutionized the approach to the patient with OGIB, either overt or occult. OGIB is the most frequent indication for CE (15). CE displays a positive safety profile and allows minimally invasive evaluation of the full length of the small bowel in a cost-effective manner (16). Similarly to scintigraphy, due to its prolonged video acquisition time, it allows for the detection of intermittent bleeding. Thus, CE is the first line for further evaluation of patients with OGIB, after previous normal conventional endoscopy (1, 17). Capsule retention, the most feared complication, occurs in 1.4% of patients (15). Adding to its exceptional tolerability and safety, CE has been shown to be an accurate diagnostic method, with high sensitivity (95%) and specificity (75%). A meta-analysis has estimated an overall diagnostic yield of CE for OGIB of almost 62% (5). Also, these values were enhanced if CE was performed early after bleeding onset or in those with overt OGIB (18-20). Factors associated with increased probability of positive CE include use of nonsteroidal anti-inflammatory drugs, diagnosis of connective tissue disease, ongoing overt bleeding, lower hemoglobin values with increased transfusion needs (20-22). Moreover, the usefulness of CE was established, providing higher diagnostic yields and reducing costs in high burden investigation of OGIB patients (16). In fact, most patients with positive CE are submitted to subsequent etiologic investigation which leads to specific therapy in up to 80% of these cases (19-21). Studies comparing diagnostic yields of different exams for the evaluation of the small bowel, either radiologic or endoscopic, indicated the overall superiority of CE. CE outperformed angiography (53% vs. 20%), CT angiography (72% vs. 56%), and push enteroscopy (63% vs. 28%) (2, 4, 23). The diagnostic yield of
CE was shown to be similar to that of the much more invasive DBE (5). Application of CE before DBE increased the diagnostic ability of the latter (5). CE may, therefore, select the patients who should be submitted to DBE, either for diagnostic or therapeutic purposes, and it may determine the ideal insertion route for DBE (1).

This is the first study to assess and correlate the diagnostic performances of CE and $^{99m}$Tc RBC scintigraphy. In fact, we aimed to evaluate the degree of concordance between scintigraphy results and the results obtained from a high diagnostic yield method with direct visualization of the small bowel. The distribution of findings with hemorrhagic potential was similar in patients with negative and positive scintigraphy and the concordance of the results of both methods was less than that expected by chance. This observation is in line with findings reported by other authors. Speir et al. reported an overall concordance of 29% between nuclear scan and angiography, and reported weaker correlation with increasing intervals between the tests (8).

Radiolabeled RBC scintigraphy does not accurately pinpoint the location of hemorrhagic foci. The blush is most frequently referred as occurring in a certain abdominal region and, from this information, a broad prediction of the bleeding source is produced. No concordance could be found between the presumed location of the bleeding on scintigraphy and the location of lesions with bleeding potential on CE. This data follows that obtained by Feuerstein et al. in which $^{99m}$Tc RBC scintigraphy performed worse than CT angiography for the precise localization of significant bleeding lesions (12). Finally, the values of hemoglobin, a surrogate marker for severity of bleeding, did not differ between patients with or without positive scans ($p = 0.058$). This may reflect the limitations of $^{99m}$Tc RBC scintigraphy in predicting the severity of hemorrhage. Duraiswamy and colleagues also did not find any differences on hematocrit values between those with positive and negative scintigraphy (9). In opposition, patients with P2 (high bleeding potential) lesions on CE had statistically significant lower levels of hemoglobin at presentation than those with P0 (no bleeding potential) lesions. Moreover, the existence of lesions with high bleeding potential moderately correlated with lower levels of hemoglobin. Similar results were obtained by other groups (18).
This study has merit in being the first to confront the diagnostic performances of scintigraphy, a widely used test, and CE, the method with the highest diagnostic yield. All exams were performed in the Gastroenterology and Nuclear Medicine Departments of the same hospital center, with highly trained medical professionals. However, this study presents several limitations: first, it is a single center retrospective study. Second, the number of included patients was relatively small, which may affect the generalizability of our results. Third, most of these patients were for iron-deficient anemia in multiple medical specialties. Therefore, medical practices regarding the request of CE or scintigraphy may have varied markedly. Third, the interval between CE and scintigraphy was large. This may have contributed for discordant findings between CE and scintigraphy. The effect of wider intervals may be particularly important for intermittent or short-lived bleedings. Moreover, therapeutic strategies implemented during this interval were not accounted for. Therefore, although a sub-analysis demonstrated similar results between those with intervals over two months and those not exceeding two months, the potential influence of this interval on the final results cannot be ignored. Finally, information regarding symptoms, current medications and other risk factors for OGIB (e.g., NSAIDs) was not systematically reported on medical files, thus hindering control for such variables.

In conclusion, this study reinforces the existing evidence questioning the role of scintigraphy for the workup of patients with OGIB. In fact, no concordance was observed between the scintigraphy results and those of a high diagnostic yield technique such as CE. The latter has proven to be an efficient diagnostic tool and the most cost-effective approach to OGIB patients. On the other hand, investigation, follow up, and treatment of patients with OGIB is rarely determined by scintigraphy results, whereas CE influences subsequent follow up for most patients. Therefore, the results presented in this study lead to question the true clinical usefulness of $^{99m}$Tc RBC scintigraphy when caring for these patients.

References


Table 1 - Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>N (%) or median (IQR)</th>
</tr>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>53 (62%)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>63 (51 – 74)</td>
</tr>
<tr>
<td>Indication for study</td>
<td></td>
</tr>
<tr>
<td>Occult OGIB, n (%)</td>
<td>73 (86%)</td>
</tr>
<tr>
<td>Overt OGIB, n (%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), median (IQR)</td>
<td>10.2 (8.9 – 10.9)</td>
</tr>
<tr>
<td>Positive scintigraphy, n (%)</td>
<td>70 (82%)</td>
</tr>
</tbody>
</table>
Capsule enteroscopy

P0, n (%) 37 (44%)
P1, n (%) 11 (13%)
P2, n (%) 37 (44%)

Lesions (n=49)

Angiectasia, n (%) 18 (37%)
Erosions, n (%) 10 (20%)
Ulcers, n (%) 6 (12%)
Petechiae, n (%) 6 (12%)
Lymphangiectasia, n (%) 5 (10%)
Other, n (%) 4 (8%)

Time between CE and scintigraphy (months), median (IQR) 4 (1.5 – 7.0)

IQR – interquartile range; OGIB – obscure gastrointestinal bleeding; CE – capsule enteroscopy.

Table 2 - Distribution of capsule enteroscopy findings according to scintigraphy results.

<table>
<thead>
<tr>
<th></th>
<th>Positive scintigraphy</th>
<th>Negative scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0, n (%)</td>
<td>32 (46%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>P1, n (%)</td>
<td>8 (11%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>P2, n (%)</td>
<td>30 (43%)</td>
<td>7 (47%)</td>
</tr>
</tbody>
</table>

Table 3 - Distribution of capsule enteroscopy and scintigraphy findings according to the intervals between both diagnostic modalities

<table>
<thead>
<tr>
<th>Interval between CE and scintigraphy</th>
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<tbody>
<tr>
<td>≤ 2 months</td>
<td>&gt; 2 months</td>
</tr>
<tr>
<td></td>
<td>Negative scintigraphy</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>P0, n (%)</strong></td>
<td>4 (40%)</td>
</tr>
<tr>
<td><strong>P1, n (%)</strong></td>
<td>2 (20%)</td>
</tr>
<tr>
<td><strong>P2, n (%)</strong></td>
<td>4 (40%)</td>
</tr>
</tbody>
</table>

**Table 4 - Median hemoglobin in scintigraphy and capsule enteroscopy**

<table>
<thead>
<tr>
<th></th>
<th>Median hemoglobin g/dL (IQR)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scintigraphy</strong></td>
<td></td>
<td>0.058</td>
</tr>
<tr>
<td>Negative</td>
<td>10.8 (9.6 – 11.8)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>10.1 (8.8 – 10.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Capsule enteroscopy</strong></td>
<td></td>
<td>0.002*</td>
</tr>
<tr>
<td>P0</td>
<td>10.6 (9.7 – 11.5)</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>10.3 (9.3 – 11.5)</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>9.3 (8.1 – 10.5)</td>
<td></td>
</tr>
</tbody>
</table>

IQR – interquartile range; *p<0.05
Figure 1 - Boxplot demonstrating median values of hemoglobin across capsule enteroscopy findings (according to Saurin's classification). Median hemoglobin of high bleeding potential lesions (P2) was significantly inferior to those with lesions without bleeding potential (P0). *p<0.05