ORIGINAL ARTICLE

AG-2016-67
dx.doi.org/10.1590/S0004-2803.2017v54n1-03

Suspected blood indicator in capsule endoscopy: a valuable tool for gastrointestinal bleeding diagnosis

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Received 25/7/2016
Accepted 10/10/2016

ABSTRACT – Background – Small bowel bleeding is a leading indication for small bowel capsule endoscopy. The Suspected Blood Indicator (SBI) is a software feature directed to automatically detect bleeding lesions during small bowel capsule endoscopy. **Objective** – We aimed to assess SBI diagnostic accuracy for small bowel haemorrhage or potentially bleeding lesions during small bowel capsule endoscopy for small bowel bleeding. **Methods –** Single-centre retrospective study including 281 consecutive small bowel capsule endoscopy performed for small bowel bleeding during 6 years. The investigators marked lesions with high bleeding potential (P2), such as angioectasias, ulcers and tumours, as well as active bleeding during regular small bowel capsule endoscopy viewing with PillCam SB2®. All small bowel capsule endoscopy were independently reviewed by another central reader using SBI. **Results** – Among the 281 patients, 29 (10.3%) presented with active haemorrhage while 81 (28.9%) presented with a P2 lesion. The most frequently observed P2 lesions were angioectasias (52), ulcers (15), polyps (7) and ulcerated neoplasias (7). SBI showed a 96.6% (28/29) sensitivity for active small bowel bleeding, with a 97.7% negative predictive value. Regarding P2 lesions, the SBI displayed an overall sensitivity of 39.5%, being highest for ulcerated neoplasias (100%), but significantly lower for angioectasias (38.5%) or ulcers (20.0%). **Conclusion –** Although SBI sensitivity for the automatic detection of potentially bleeding lesions was low, it effectively detected active small bowel bleeding with very high sensitivity and negative predictive value.

HEADINGS – Capsule endoscopy. Small intestine. Gastrointestinal hemorrhage.

INTRODUCTION

Small bowel bleeding (SBB) has been recently defined as bleeding within the gastrointestinal tract that recurs or persists after an initial negative endoscopic study (esophagogastroduodenoscopy and colonoscopy)[10,23]. SBB may be further characterized as overt (such as melena or hematochezia) or occult (iron deficient anaemia or positive faecal occult blood test)[12], and comprises a small (5%) but significant fraction of gastrointestinal bleeding[15].

Small bowel capsule endoscopy (SBCE) revolutionized small bowel diagnosis, and established itself as the first line procedure in patients presenting with SBB[3,12], presenting with a diagnostic yield of 40%-60%[1,2], superior to that of push enteroscopy, computed tomography and angiography[16,21].

One of the chief limitations in SBCE is the significant reading time needed for the thorough review of the entire small bowel – previously published studies report a median reading time ranging from 17 to 120 minutes to observe the 50.000 images captured by the device[8,22]. This limitation is of particular interest for indications such as overt SBB, when the timely diagnosis and treatment is of paramount relevance[19].

RAPID reader® (Given Imaging, Yokneam, Israel) includes several software functionalities designed to assist the gastroenterologist for a faster and more efficient video revision, such as a multiframe viewing system[7], virtual chromoendoscopy FICE® mode to highlight surface patterns and mucosal lesions[6,9], the algorithm Quickview® that compresses the video by identifying the most distinct images and hiding similar patterns[11] and finally, the suspected blood indicator® (SBI), where frames with red-coloured pixels are tagged and considered for revision[14]. SBI is easily assessable during SBCE video review, and may be found under the "Tools" tab (Figure 1).

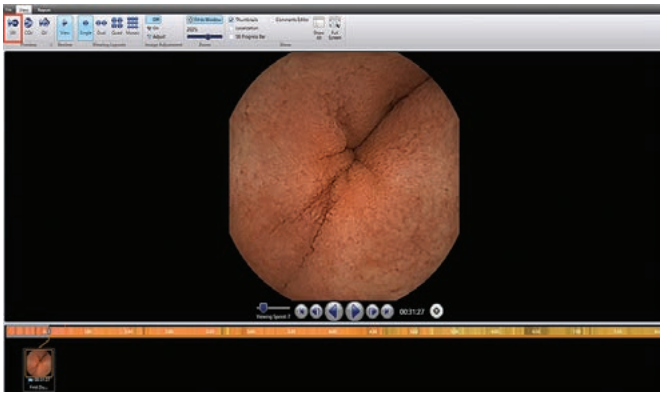

FIGURE 1. Suspect blood indicator (red square) with the RAPID® Software

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
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The SBI was designed to readily identify both small bowel haemorrhage as well as potentially bleeding lesions; however, the reports on the usefulness of this tool are scarce. Liangpunsakul et al.[13] first analyzed the diagnostic accuracy of SBI for small bowel lesions in a small group of 24 patients, and found a sensitivity of over 80% for actively bleeding lesions, but only 25% for potentially bleeding lesions such as angioectasias, ulcers and erosions. Further studies with small sample sizes reported similar values for both non-actively bleeding lesions[2,7] as well as small bowel haemorrhage[18,20], while some authors report on the usefulness of SBI in settings other than SBB, such as suspected Crohn's Disease[2].

We aimed to evaluate the diagnostic accuracy of SBI for small bowel haemorrhage or potentially bleeding lesions in both overt and occult SBB in the largest patient series to date, when compared to a blinded conventional review of the SBCE performed by an experienced gastroenterologist.

METHODS

We performed a retrospective single-centre study including all patients presenting with SBB who underwent SBCE in our department during a 6-year period (between January 2008 and December 2013). All patients had written informed consent for SBCE examination. The study was previously approved by our institution ethics committee. In every patient, an EGD and colonoscopy were performed prior to the SBCE (interval <6 months), which were non-diagnostic. SBB was classified as visible when the patient presented with either melena or haematochezia, and occult if there was iron deficient anaemia (Haemoglobin <13 g/dL for men, <12 g/dL for women) or a positive faecal occult blood test. The PillCam SB2® (Given Imaging, Yoknеam, Israel) was used. Patients were instructed to ingest only clear liquids on the day prior to the exam, as well as adhere to a 12 hour fast; no additional bowel preparation was employed. Domperidone was used (10 mg) if the SBCE remained in the stomach for over 1h (assessed through real-time viewing)[4].

Four gastroenterologists with experience in SBCE (>100 examinations), whose inter-observer percentage of agreement was previously shown to be near-perfect[5,6] reviewed the exams using conventional viewing (reading speed was defined as 10-12 fps in single image view for all patients). Another expert (>250 SBCE examinations), blinded to the initial capsule findings, marked down all SBI findings.

Only small bowel lesions were considered, and described using the commonly employed classification of Saurin et al.[17], as P0 (no bleeding potential, such as nodules and lymphangiectasias), P1 (uncertain bleeding potential, such as red spots or small erosions) and P2 (high bleeding potential, such as angioectasias, ulcers, tumors or varices).

For the sensitivity analysis, an SBI finding was not considered per frame, but per lesion, such that an angioectasia marked on 3 SBI frames was considered as 1 positive result. Also, because the clinical significance of P1 lesions has been increasingly questioned[17,19] and there is paucity of directed therapeutical approach to small bowel erosions, we defined only P2 lesions and active bleeding when considering SBI performance. We followed a methodology similar to previous studies[7,18] where a true positive result was defined if the SBI marked at least one P2 lesion and all active bleeding, a false positive if the SBI marked any frame in a SBCE without either a P2 lesion or active bleeding, a false negative if the SBI missed any active bleeding or all P2 lesions, and a true negative if the SBI marked no frame in a negative SBCE.

Statistical analysis was performed using SPSS 21.1™ (WinWrap Basics™). Univariate analyses were performed, using independent samples *t* test for continuous variables and the $\chi 2$ or Fisher's exact tests for categorical variables. Statistical significance was defined for *P*-value <0.05.

RESULTS

A total of 281 patients performed SBCE for SBB between January/2008 and December/2013 and were included. Mean patient age was 62.1 years (SD±18.1 years), 63.0% (n=177) were female, and the majority (81.9%; n=230) presented with occult SBB, while 18.1% (n=51) were referred for SBCE for overt SBB.

During conventional video review, P2 lesions were found in 81 (28.9%) patients: ulcers in 15, angioectasias in 52, polyps in 7 and ulcerated neoplasias in 7 patients; P1 lesions in 57 (20.3%) patients: erosions in 38, red spots in 19; P0 lesions (lymphangiectasias) were found in 4 (1.4%) patients; small bowel active haemorrhage was identified in 29 (10.3%) patients, and the causative lesions were identified in 9 (31.0%) of them (six angioectasias, two ulcerated neoplasias, one ulcer). SBCE findings according to indication (overt or occult SBB) can be found on Table 1.

TABLE 1. SBI Findings for indication

	Occult OGIB (n=230)	Overt OGIB (n=51)
No lesions	123 (53.5)	20 (39.2)
P0	3 (1.3)	1 (2.0)
Lymphangiectasias	3 (1.3)	1 (2.0)
P1	41 (17.8)	16 (31.7)
Red Spots	14 (6.1)	5 (9.8)
Erosions	27 (11.7)	11 (21.6)
P2	66 (28.7)	15 (29.4)
Angioectasias	44 (19.1)	8 15.7)
Ulcers	10 (4.3)	5 (33.3)
Polyps	6 (2.6)	1 (2.0)
Neoplasia	6 (2.6)	1 (2.0)
Active bleeding	21 (9.1)	8 (15.7)

P0: no bleeding potential, such as nodules and lymphangiectasias; P1: uncertain bleeding potential, such as red spots or small erosions; P2: high bleeding potential, such as angioectasias, ulcers, tumors or varices.

SBI detected luminal blood in 28 (96.6%) of the 29 patients with active small bowel bleeding and successfully marked 32 (39.5%) out of the 81 patients with P2 lesions. In respect to individual lesions, SBI detected 3 (20.0%) in 15 patients with small bowel ulcers, 20 (38.5%) in 52 angioectasias, 2 (28.6%) in 7 patients with polyps

and 7 (100%) in 7 patients with ulcerated neoplasias – Figure 2. The rate of false positive results with SBI was 76.5% – SBI marked a red frame in 215 of the 281 patients, and in all of them there was at least one area where no haemorrhage or potentially bleeding lesion was observed – therefore, when considering the examination of the entire small bowel, the accuracy for SBI for the detection of either haemorrhage or potentially bleeding lesions was 49%.

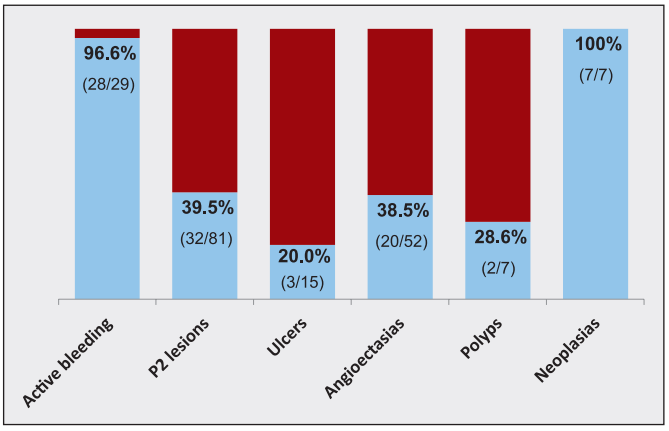

FIGURE 2. Suspected Blood Indicator sensitivity for small bowel active bleeding and P2 lesions

SBCE thumbnails captured using SBI may be found in Figures 3A-3C, including active small bowel bleeding (Figure 3A), angioectasia (Figure 3B), and a false positive result arising from the presence of bubbles in the lumen (Figure 3C). A false negative result of the SBI, an ulcer observed during conventional review, is found in Figure 3D.

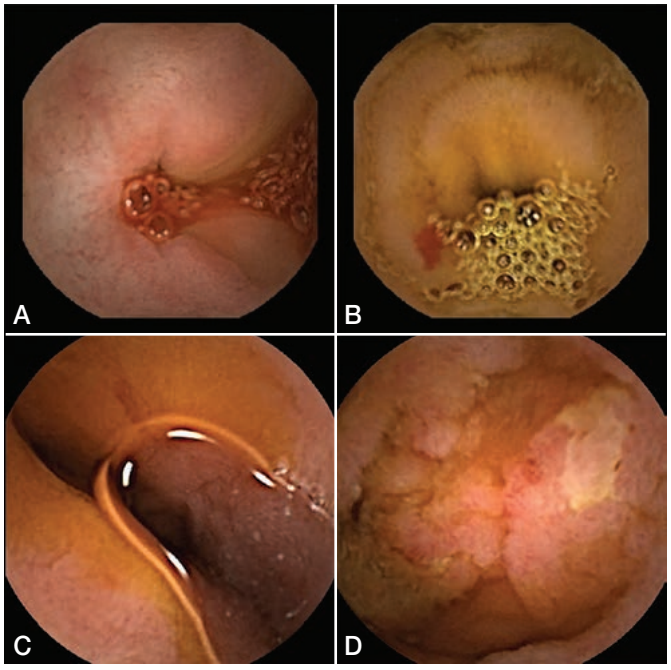

FIGURE 3. A. Active bleeding in small bowel capsule endoscopy. B. Small bowerl angioectasia in small bowel capsule endoscopy. C. False positive (air bubble) of suspected blood indicator. D. False negative (ulcer) of suspected blood indicator.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for SBI regarding each P2 lesion and active small bowel bleeding can be found in Table 2.

TABLE 2. Performance Characteristics of the Suspected Blood Indicator for P2 lesions and active small bowel bleeding

Small bowel lesion	P2 (overall)	Angioectasia	Ulcer	Polyp	Neoplasia	Haemorrhage
Sensitivity (%)	39.5	38.5	20.0	28.6	100.0	96.6
Specificity (%)	51.2	53.9	56.3	57.4	57.2	17.1
PPV (%)	19.0	14.1	2.6	1.8	7.0	11.8
NPV (%)	74.5	81.2	92.2	96.6	100.0	97.7

DISCUSSION

Despite presenting itself as the first line diagnostic procedure for SBB evaluation[12], SBCE review is often hindered by the substantial amount of time needed for entire small bowel visualization[22], which may be of particular importance in the presence of active small bowel haemorrhage[19]. The SBI tool, included in the RAPID reader® software (Given Imaging, Yokneam, Israel), allows for a significant reduction of the reviewing duration from up to some hours to a few minutes[8,22], marking red areas identified by an algorithm as either active bleeding or potentially bleeding lesions.

In our study, we include the largest published series to date comparing SBI with conventional visualization by an experienced reader, comprising 281 patients, to assess its usefulness at detecting major small bowel abnormalities, as well, and more importantly, to readily detect small bowel haemorrhage.

We encountered 29 instances of small bowel bleeding, and SBI was positive for all but one of them, resulting in a sensitivity of 96.6% and a NPV of 97.7%, and highlighting the performance of SBI for quickly screening small bowel active haemorrhage. These results are superior to the ones reported by D'Halluin et al. (sensitivity of 83.0%)[7], Liangpunsakul et al.[13] (sensitivity of 81.2% and NPV of 85.0%), Buscaglia (sensitivity of 58.3%)[2] or Signorelli (sensitivity of 60.9% and NPV of 76.3%)[18] but similar to the ones encountered more recently by Tal et al. (sensitivity of 100%, NPV of 87.2%)[20]. This discrepancy may be explained by the progressive improvements for the SBI detection algorithm in RAPID reader® up to version 6.0[8], allowing for an improved detection performance in the more recent studies[20].

SBI missed the detection of an active haemorrhage in 1 of our 29 patients, a low intensity duodenal bleeding on the background of a frankly erythematous mucosa. The relevance of the background tonality for the SBI detection rate was recently explored in an experimental study by Park et al.[14] – in this study, a red area detection rate was highest in a pale magenta background – equivalent to a pale small bowel mucosa (42.7%), two times better than when the background was dark greyish pink – erythematous mucosa (24%), and almost four times better than when the background was deep brown – presence of luminal bile pigment (12.0%). These results suggest that SBI is more likely to detect a small bowel red area in the presence of significant anaemia while poor bowel preparation or the presence of erythematous mucosa should alert the clinician to perform a careful inspection even with negative SBI[14]. Finally, in all the nine cases of patients with small bowel bleeding detected by the SBI where the investigator identified

a causative lesion (six angioectasias, two ulcerated neoplasias, one ulcer), SBI detected both the bleeding and the P2 lesion, proving itself as a quick and sensitive method for the detection of actively bleeding small bowel lesions.

Regarding small bowel lesions with high bleeding potential (P2), the results with SBI are unsurprisingly not as satisfactory. SBI sensitivity for P2 lesions was 39.5%, with a negative predictive value of just 74.5% – one quarter of the patients with at least one P2 lesion would be missed using only SBI for the SBCE review. The sensitivity was broadly different among P2 lesions, from up to 100% (7/7) for ulcerated neoplasias, 38.5% (20/52) for angioectasias, 28.6% (2/7) for polyps, and down to just 20% (3/15) for small bowel ulcers.

SBI sensitivity for angioectasias in our study was comparable to the one reported by D'Halluin et al. (40.6%)[7] and Signorelli et al. (25.8%)[18] but frankly superior to both Buscaglia et al. (16.3%)[2] and Liangpunsakul et al. (12.7%)[13]. Since angioectasias are clearly defined red lesions, the reasons for such heterogeneity may be related either to a type II error in small sample-sized studies, or perhaps reader bias, as some interobserver variability may occur in the interpretation of small bowel red spots (P1 lesions) versus minor angioectasias.

None of the previous studies with SBI included neoplastic lesions in the SBI performance assessment, probably due to reduced sample sizes, but we encountered seven polyps and seven ulcerated neoplasias in our patients. The excellent sensitivity of SBI for ulcerated neoplasias is expected, since the algorithm selects abnormal red coloration in a defined area, and the larger the lesion, the most likely it is to be detected; most neoplasias spanned several frames in a large area of the image, allowing the recognition by the SBI. On the other hand, however, small bowel polyps, often with colour tonality similar to normal mucosa, are unlikely to be marked by the SBI, since the algorithm has no recognition capability for protruding lesions, but solely different colour patterns.

Finally, we report an average false positive rate for SBI of 76.5% – despite high, the fact that reviewing and analyzing the subset of frames marked by the SBI is fast, and the identification of true positive results is readily apparent, the clinical impact of this finding is marginal.

In conclusion, SBI was able to detect almost all instances of small bowel active bleeding, as well as almost 40% of small bowel lesions with high bleeding potential in this large series of patients. Despite some limitations, such as the high rate of false negative results in important and frequent findings, remarkably ulcers and angioectasias, SBI was shown to swiftly detect and identify small bowel haemorrhage, assisting the reader in a fast review of the most important SBCE findings, a crucial process in the emergency setting.

Authors' contributions

Carvalho PB carried out the study, data analysis, did literature search and drafted the manuscript; Magalhães J, Castro FD, Monteiro S reviewed the videos of capsule endoscopies; Moreira MJ participated in the design of the study and reviewed the videos of capsule endoscopies; Rosa B revised the manuscript and centrally reviewed the videos of capsule endoscopies; Cotter J critically revised the manuscript and approved the final version to be submitted. The study was approved by the Institutional Ethics Committee.

Boal Carvalho PB, Magalhães J, Dias de Castro F, Monteiro S, Rosa B, Moreira MJ, Cotter J. "Suspected Blood Indicator" na enteroscopia por cápsula: uma ferramenta útil no diagnóstico de hemorragia gastrointestinal. Arq Gastroenterol. 2017,54(1):16-20.

RESUMO – Contexto – A hemorragia do intestino delgado é uma das principais indicações para a realização de enteroscopia por cápsula. A ferramenta "Suspected Blood Indicator (SBI)", incluída no software de leitura da enteroscopia por cápsula, tem como objetivo a deteção automática de hemorragia e de lesões potencialmente hemorrágicas. **Objetivo –** Pretendemos avaliar a acuidade diagnóstica do SBI para a deteção de hemorragia ou lesões potencialmente hemorrágicas durante a enteroscopia por cápsula no contexto de hemorragia do intestino delgado. **Métodos –** Estudo retrospectivo incluindo 281 enteroscopia por cápsula (PillCam SB2®) consecutivas realizadas por hemorragia do intestino delgado durante 6 anos. Os investigadores registaram lesões com potential hemorrágico elevado (P2), como angiectasias, úlceras e neoplasias, assim como hemorragia activa. Todos os exames foram revistos independentemente por outro investigador, utilizando o SBI. **Resultados –** Dos 281 doentes, 29 (10,3%) apresentaram hemorragia ativa, enquanto 81 (28,9%) apresentaram uma lesão P2. As lesões P2 mais frequentes foram angiectasias (52), úlceras (15), póipos (7) e neoplasias ulceradas (7). O SBI demonstrou uma sensibilidade de 96,6% (28/29) para hemorragia activa, com um valor preditivo negativo de 97,7%. Para as lesões P2, a sensibilidade global foi de 39%: 100% para neoplasias ulceradas, 38,5% para angiectasias e 20% para úlceras. **Conclusão –** Apesar da sensibilidade do SBI para lesões potencialmente hemorrágicas do instestino delgado ser baixa, permitiu a deteção de hemorragia activa com uma muito elevada sensibilidade e excelente valor preditivo negativo.

DESCRITORES – Endoscopia por cápsula. Intestino delgado. Hemorragia gastrointestinal.

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