Improving Diagnostic Yield of Capsule Endoscopy in Coeliac Disease: Can Flexible Spectral Imaging Colour Enhancement Play a Role?

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Keywords

Flexible spectral imaging colour enhancement · Small bowel capsule endoscopy · Coeliac disease

Abstract

Introduction: Flexible spectral imaging colour enhancement (FICE) is a form of virtual chromoendoscopy that is incorporated in the capsule reading software and that can be used by reviewers to enhance the delineation of lesions in the small bowel. This has been shown to be useful in the detection of pigmented (ulcers, angioectasias) lesions. However, its application to coeliac disease (CD) images from small bowel capsule endoscopies (SBCEs) has rarely been studied.

Methods: This was a European, multicentre study that included 5 expert capsule reviewers who were asked to evaluate a number of normal and abnormal de-identified images from SBCEs of patients with CD to determine whether the use of FICE and blue light can improve the detection of CD-related changes. **Results:** Sensitivity and specificity of conventional white light in the delineation of CD-related changes were 100%. The next best image modification was FICE 1 with a sensitivity of 80% and a specificity of 100%. There was no difference between conventional white light, FICE and blue light for the identification of CD-related changes. There was a low agreement (Fleiss kappa 0.107; $p = 0.147$) between

expert reviewers in selecting the best image modification that detected CD-related changes. **Conclusions:** FICE and blue light were not found to be superior to conventional white light in the delineation of macroscopic changes related to CD on SBCEs.

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Introduction

Although most guidelines on adult coeliac disease (CD) recommend gastroduodenoscopy and duodenal biopsies in patients with positive CD serology and suggestive symptoms [1, 2], some patients are unwilling to undergo this procedure to establish a definitive diagnosis of CD. Small bowel capsule endoscopy (SBCE) can play a useful role in this cohort of patients [3]. Even in patients undergoing a gastroduodenoscopy and duodenal biopsies, pitfalls in the diagnosis of CD still exist mainly due to the patchy nature of CD [4–6]. Unless at least 4 biopsy specimens (including a duodenal bulb biopsy) are taken from the duodenum [2, 4] and the samples are properly oriented during preparation for histological assessment [7], duodenal biopsy sampling may be sub-optimal. These factors establish a further role for SBCE in patients with a high suspicion of CD but negative duodenal histology,

due to its panoramic underwater view that magnifies changes in the small bowel (SB) and improves delineation of lesions.

Over the years, attempts have been made to improve the detectability of pathological lesions on SBCE. One such modality is the application of flexible spectral imaging colour enhancement (FICE), a form of virtual chromoendoscopy. It can be applied to images from SBCE by adjusting settings on the RAPID reading software [8]. As the capsule travels through the SB, images in the white light spectrum are captured. Post-production computer algorithms then select single wavelength images in the red, green and blue spectra to reconstruct FICE enhanced images [9, 10]. The aim is to improve the detection of mucosal changes such as the delineation of small blood vessels, enhance the resolution of mucosal patterns and augment colour differences [11]. Blue light is an additional image-enhancing setting available on the RAPID software that enables light in the wavelength range of 490–430 nm to be picked up from white light images.

Macroscopic changes of CD occur secondary to different degrees of villous atrophy resulting in scalloping of folds, fissuring and mosaic pattern of mucosa. Other features include complete absence of villi giving the appearance of villous atrophy. Ulcers can also be present at times [12, 13]. These changes can be identified on conventional white light SBCE. However, the detection of findings can be challenging due to subtle changes only affecting the duodenal bulb in ultra-short CD [14]. The manifestation of CD is also often patchy in nature [6]. Image modification to enhance features of CD may help the delineation of CD-related changes particularly for novice SBCE reviewers. There is only one study that reports on the use of FICE for the detection of changes related to CD in the SB. However, only one macroscopic feature – villous atrophy was studied and the same cohort included patients with other pathologies apart from CD [15]. Our study is the first to report on the utility of FICE and blue light in a cohort of patients with CD alone on SBCE.

The sensitivity of SBCE in detecting CD-related changes is reported to be as low as 70% in some studies [16]. The sensitivity of SBCE depends on the reviewer's pre-study experience declining when the reviewer's pre-study experience is low [16]. Changes related to CD in the SB can vary from very mild to more severe features. Subtle changes can contribute to decreasing the sensitivity of SBCE to detect CD-related changes. The aim of this study was to assess whether there is any additional benefit in using FICE or blue light over conventional white light for the detection of changes related to CD on SBCE.

Methods

Patients and Methods

This was a multicentre, European study that included 5 expert capsule endoscopy reviewers (>300 capsules/year). They were asked to evaluate a number of de-identified images from SBCEs of patients with confirmed CD on duodenal histology to determine whether the use of FICE and blue light can improve the detection of CD-related changes on SBCE. Features of CD on SBCE images and normal SBCE images were initially identified and features of CD confirmed by 2 expert SBCE reviewers (>300 capsules/year). These 2 expert reviewers involved in the initial preparation of the images were not involved in the actual study. Findings on these images were then set as the standard to which results from each reviewer were compared to. Features of CD included: (1) scalloping of the mucosa, (2) fissuring of folds, (3) mosaic pattern, (4) villous atrophy, (5) nodularity of mucosa. The reviewers were blinded to each other's findings and to the histological Marsh classification of disease.

In the first part of the study, the reviewers were asked to examine a set of 50 images consisting of both normal (25) SB images and 25 images showing CD-related changes. Conventional white light, FICE I, II, III and blue light were represented in 1 question each in this section. Each question consisted of 5 normal and 5 abnormal images from the SBCE of the same patient (Fig. 1). The reviewers were asked to pick up abnormal images (Which images show features of CD?). Depending on the number of abnormal images correctly picked up by each reviewer, the sensitivity and specificity of conventional white light, different FICE settings and blue light were calculated.

In the second part of the study, reviewers were asked to go through 55 abnormal images (11 questions) and to compare between conventional white light, different FICE (I, II, III) settings and blue light as the best modality to delineate changes of CD on SBCE. Each question consisted of abnormal images in conventional white light, different FICE settings or blue light (Fig. 2). Images showed either moderate (5 questions), severe features of CD (5 questions) or ulcers (1 question). Severity of features on each image were pre-determined by an expert SBCE reviewer (>300 capsules/year) before the commencement of this study depending on the presence of patchy/continuous pattern and prominence of lesions. This was confirmed by a second SBCE reviewer (>300 capsules/year). The interobserver agreement between reviewers was then calculated.

Ethics Approval

The study protocol was approved by the Yorkshire and Humber Research Ethics Committee (IRAS 232382) and registered with the local research and development department of Sheffield Teaching Hospital NHS Foundation Trust under the registration number STH 19998. All images used in this study were de-identified. No additional consent was required for the study with the use of de-identified videos as assessed and approved formally by the Research Ethics Committee.

Statistical Analysis

IBM SPSS Statistics version 23 and Microsoft Excel for Mac version 16.16.4 were used to analyse the data. Frequencies of choice were calculated for each expert reviewer. Fleiss' kappa coefficient (K) was used to measure the degree of agreement amongst the 5 reviewers. Agreement according to K value was considered

Fig. 1. Images on SBCE modified by FICE 2 (**b–d, f, h**) show features of CD (**a, e, g, i, j**) are normal images.

as follows: <0 indicated poor agreement, 0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement [17]. A significance level of >0.05 ($p > 0.05$) meant that there was not enough evidence to conclude that the reviewers'

agreement was different from what would be expected to be achieved by chance.

Contingency tables were also constructed to calculate the sensitivity and specificity of conventional white light, different FICE settings and blue light.

Fig. 2. Fissuring of mucosa in a patient with CD on SBCE: (a) conventional white light; (b) FICE 1; (c) FICE 2; (d) FICE 3; (e) blue light.

Power Calculation

Currently, the sensitivity of SBCE in detecting CD-related changes using conventional white light, varies between 70 and 93% [3, 16, 18–22]. To improve the sensitivity of SBCE from the lowest recorded value of 70.0–93.0% by the introduction of FICE on reviewing SBCE images, (using G Power) it was estimated that a sample size of 28 would be needed to correctly identify changes of CD with 95% power and a 5% 2-sided significance level. We have exceeded the required number to reach the 95% power in both sections of the study.

Our study is the first to report on the utility of FICE and blue light in a cohort of patients with CD alone on SBCE.

Results

All patients had duodenal atrophy (Marsh 3a: 18.8% [$n = 3$], Marsh 3b: 50% [$n = 8$], Marsh 3c: 31.3% [$n = 5$]) on biopsies taken from the second part of the duodenum. All reviewers identified the abnormal images in conventional white light resulting in 100% sensitivity and specificity. FICE 1 had the next best sensitivity in the identification of abnormal images followed by sensitivities for FICE 2 and 3. Blue light had the lowest sensitivity in detecting features of CD (Table 1).

Although FICE 1 and 2 were the most popular settings chosen by reviewers to delineate changes of CD in the

second section, there was no statistically significant difference between reviewers ($p = 0.193$; Table 2). The low overall K ($K = 0.107$; $p = 0.147$) was consistent with poor correlation of the preferred modality amongst different expert reviewers (Table 3). The overall K were similarly low for moderate ($K = 0.107$; $p = 0.147$) and severe ($K = 0.107$; $p = 0.147$) changes of CD. The K was low even when considered separately for different light settings and it was not statistically significant in all cases (conventional white light $K = -0.122$, $p = 1.801$, FICE 1 $K = 0.189$, $p = 0.148$, FICE 2 $K = 0.149$, $p = 0.255$). None of the reviewers favoured FICE 3 and blue light. Therefore, these have been left out of Tables 1 and 2. This also means that the K could not be calculated for FICE 3 and blue light.

Discussion

This study confirms that FICE and blue light do not have any additional benefit in helping the delineation of CD changes on SBCE when compared to conventional white light.

Dye chromoendoscopy has been utilised in the context of IBD surveillance to help the visualisation of subtle lesions and to define surface staining patterns enabling

Table 1. Mean sensitivity, specificity, positive and negative likelihood ratios for normal light, FICE and blue light

	Conventional white light, %	FICE 1, %	FICE 2, %	FICE 3, %	Blue light, %
Reviewer 1	100	80	60	0	40
Reviewer 2	100	80	100	100	60
Reviewer 3	100	80	60	60	20
Reviewer 4	100	60	60	40	20
Reviewer 5	100	100	100	100	100
Mean sensitivity	100	80	76	60	48
Reviewer 1	100	100	100	100	100
Reviewer 2	100	100	100	100	100
Reviewer 3	100	100	100	100	100
Reviewer 4	100	100	80	60	80
Reviewer 5	100	100	100	100	100
Mean specificity	100	100	96	92	96

FICE, flexible spectral imaging colour enhancement.

Table 2. Favoured modality of normal light or different FICE settings by all the 5 reviewers

Severity of changes	Conventional white light, n (%)	FICE 1, n (%)	FICE 2, n (%)
<i>Mild</i>			
1. Which capsule endoscopy image shows fissuring of the mucosa best?	0	4 (80)	1 (20)
2. Which capsule endoscopy image shows scalloping of the mucosa best?	1 (20)	1 (20)	0
3. Which capsule endoscopy image shows villous atrophy best?	1 (20)	3 (60)	0
4. Which capsule endoscopy image shows nodularity of the mucosa best?	0	3 (60)	2 (40)
5. Which capsule endoscopy image shows mosaic pattern of the mucosa best?	1 (20)	0	1 (20)
<i>Moderate</i>			
6. Which capsule endoscopy image shows fissuring of the mucosa best?	0	3 (60)	2 (40)
7. Which capsule endoscopy image shows scalloping of the mucosa best?	1 (20)	3 (60)	1 (20)
8. Which capsule endoscopy image shows villous atrophy best?	0	5 (100)	0
9. Which capsule endoscopy image shows nodularity of the mucosa best?	1 (20)	1 (20)	3 (60)
10. Which capsule endoscopy image shows mosaic pattern of the mucosa best?	1 (20)	1 (20)	3 (60)
<i>Ulcers</i>			
11. Which image shows ulceration of the mucosa best?	0	4 (20)	1 (20)

FICE, flexible spectral imaging colour enhancement.

targeted biopsies to be taken [23]. Virtual chromoendoscopy has been applied to identifying adenomatous polyps and areas of dysplasia during upper GI endoscopy and in helping the identification of polyps during colonoscopy [24, 25]. It has also been shown to be useful in detecting high-grade dysplasia in Barrett's epithelium [26].

The use of FICE to aid reporting of SBCE has been widely debated in the context of SB ulcers and vascular lesions. FICE can improve the detection of ulcerative lesions by highlighting inflammatory halos and increasing the contrast between pathological areas and surrounding

mucosa [8, 15, 27–31]. Whilst some early studies showed that FICE performed better than conventional white light for the detection of SB ulcers, other studies have contradicted this finding [32].

FICE has also been studied for the detection of angioectasias with some studies showing benefit [8, 15, 28–30, 32, 33]. This is because it improves the detection of light in certain spectrums that is absorbed by haemoglobin. In 2 studies on patients with obscure gastrointestinal bleeding, patients with negative SBCEs in standard view were enrolled. FICE was able to detect significant lesions in

Table 3. Fleiss' kappa co-efficient for normal light and FICE settings

	Total	Conventional white light	FICE 1	FICE 2
K	0.107	-0.122	0.189	0.149
SE	0.073	0.095	0.129	0.129
Z	1.451	-1.284	1.447	1.151
P	0.147	1.801	0.148	0.250
Lower	-0.037	-0.309	-0.066	-0.104
Upper	0.250	0.064	0.440	0.402

FICE, flexible spectral imaging colour enhancement; SE, standard error.

5.8–21% of patients [34, 35]. However, FICE has been shown to have a high false-positive rate in the delineation of angioectasias [36].

This is the first and largest study on the use of FICE and blue light to help delineate changes related to CD on SBCE. In this study, experts were asked to determine which FICE setting, blue light or conventional white light was the best modality to detect mucosal abnormalities. Both FICE and blue light were inferior to conventional white light in detecting CD changes on SBCE images. The calculation of sensitivity and specificity of FICE add further to the current evidence on FICE when compared to conventional white light. The sensitivity and specificity of detecting SB pathologies using FICE were similar to conventional white light in a study by Kobayashi et al. [37]. Similarly, the sensitivity and specificity of FICE in detecting CD-related lesions in this study were similar in the case of FICE 1, 2, and 3 but inferior to conventional white light.

The low K co-efficient confirms the lack of agreement between reviewers to favour any FICE settings or blue light in the detection CD changes on SBCE. K co-efficient was low irrespective of the severity of CD changes on SBCE suggesting that FICE will not help increase the detection of CD changes on SBCE even if the changes are subtle.

Our findings on the use of FICE on SBCE images to help detect features of CD reflect literature previously published on the use of dye chromoendoscopy during gastroduodenoscopy to improve the detection of macroscopic features of CD [38]. In the study by Johnston et al. [38], chromoendoscopy identified an additional number of patients with CD (54% with chromoendoscopy vs. 42% on normal endoscopy) on gastroduodenoscopy. However, the sensitivity of chromoendoscopy was by far inferior to the sensitivity of CD serology (89% anti-tissue transglutaminase antibody, 78% for anti-endomysial anti-

body). Thus, it was concluded that chromoendoscopy could not be recommended for routine clinical practice during gastroduodenoscopy in patients with suspected and established CD.

One limitation of this study is the exclusion of mild macroscopic CD-related changes due to the assumption that these would have been much harder to delineate, thus impacting negatively on the degree of agreement between expert reviewers. It was assumed that all the expert reviewers had the same pre-study experience of reviewing SBCEs from patients with CD. Inclusion of a section prior to this study, with images to ensure familiarisation of expert reviewers with macroscopic CD-related changes on SBCEs might have resulted in an improvement in the agreement between reviewers.

In a recent meta-analysis, the delineation of SB pathologies using FICE was studied [39]. The meta-analysis included 3 studies that assessed the improvement in delineation of lesions and 5 studies that evaluated the detection of lesions. Overall, FICE did not help to improve the detection of SB lesions except for pigmented lesions where FICE performed better. FICE 1 setting improved the delineation of 89% of angioectasias and 45% of ulcers and erosions. The recently published ESGE technical guidelines [40] do not recommend the routine use of virtual chromoendoscopy during SBCE as this does not improve the delineation of lesions. This statement mainly refers to vascular and ulcerative lesions, since studies referring to images taken from SBCE of patients with CD are lacking.

Only one group of authors has studied the role of FICE in the detection of CD-related changes. Two gastroenterologists, blinded to each other's results, were asked to rank the quality of delineation of SB pathologies as better, equivalent, or worse than conventional white light. FICE 1 and 2 improved the detection of villous atrophy with a high K between expert reviewers [15]. There are considerable differences between the way this study was conducted and our methodology. Cotter et al. [15] included other SB pathologies in their study apart from CD-related changes including angioectasias and ulcers unlike in our case where the main focus was on CD. Cotter et al. [15] only considered oedema and villous atrophy but did not assess the effect of FICE on the delineation of other macroscopic features of CD. They also asked reviewers to grade FICE images as better, equivalent or worse compared to conventional white light unlike in our case where a comparison of different FICE settings and conventional white light was done for each question. Having only 2 images to choose from might explain the much higher K values obtained in this study unlike in our study where

the agreement between reviewers was very poor. In addition, a greater number of expert reviewers were included in our study.

Narrowing the bandwidth with FICE enhances the hypervascularity of lesions. Most of the macroscopic changes of CD occur due to various degrees of villous shortening and not due to vascular changes [41]. This can explain the lack of additional benefit of FICE on SBCE in patients with CD.

Data on the use of FICE and blue light are very sparse and at times contradictory. Some studies evaluate the use of FICE on multiple pathologies that can exist in the SB resulting in evaluation of virtual chromoendoscopy in even smaller groups of patients. Authors have used different methodologies to evaluate the use of FICE, making it harder to compare results between studies and questioning further the utility of FICE.

Despite the negative results of this study, the results are useful as they add to the limited literature that is available on the use of FICE on SBCE in suspected CD. They provide evidence that there is no additional benefit for gastroenterologists to re-review SBCE in different FICE settings or blue light after reviewing the SBCE using conventional white light when the suspicion of CD is high. The use of FICE will not help in the detection of subtle CD-related changes by novice SBCE reviewers.

Conclusions

This study has demonstrated that amongst 5 expert SBCE reviewers, FICE settings and blue light were not better than conventional white light in the identification of macroscopic changes of CD. Reviewing SBCE images with different FICE settings where CD is suspected will not help to delineate these changes better.

Statement of Ethics

The study protocol was approved by the Yorkshire and Humber Research Ethics Committee (IRAS 232382) and registered with the local research and development department of Sheffield Teaching Hospital NHS Foundation Trust under the registration number STH 19998.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

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