

Use of small bowel capsule endoscopy in patients with chronic kidney disease: experience from a University Referral Center

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Abstract

Background There are only few reports on the diagnostic yield (DY) of small bowel capsule endoscopy (SBCE) in patients with chronic kidney disease (CKD). We aim to report our SBCE experience in patients with CKD.

Methods Retrospective study; case notes of patients with low estimated glomerular filtration rate (eGFR) who underwent SBCE (March 2005-August 2012) for anemia and/or obscure gastrointestinal bleeding (OGIB) were retrieved and abstracted. Severity of CKD was defined according to Renal Association recommendations as: stage 3 (eGFR: 30-59); stage 4 (eGFR: 15-29); and stage 5 (eGFR <15 or on dialysis).

Results In the aforementioned period, 69 patients with CKD [stage 3: 65/69 (92.8%), stage 4 or 5: 4/69 (7.2%)] had SBCE. 51/65 (78.5%) patients with stage 3 CKD had SBCE due to unexplained anemia and/or OGIB [43 (66.1%) and 8 (12.3%), respectively]. In 25/51 (49%), the SBCE was normal and in 17/51 (33.3%) showed small-bowel angiectasias. Other findings were active bleeding (n=2), fold edema (n=2), ileal erosions (n=1), adenocarcinoma (n=1), and inconclusive/videos not available (n=3). All patients (n=4) with CKD grade 4 or 5 were referred due to unexplained anemia; 3/4 (75%) had angiectasias and 1 normal SBCE. Fecal calprotectin (FC) was measured in 12 patients with CKD stage 3 and unexplained anemia prior to their SBCE; no significant small-bowel inflammation was found in this subgroup.

Conclusion SBCE has limited DY in CKD patients referred for unexplained anemia. Sinister SB pathology is rare, while the most common finding is angiectasias. Furthermore, FC measurement prior to SBCE -in this cohort of patients- is not associated with increased DY.

Keywords Capsule endoscopy, chronic kidney disease, obscure gastrointestinal bleeding, anemia, fecal calprotectin

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Introduction

Patients with poor renal function frequently present with

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gastrointestinal (GI) complications such as obscure GI bleeding (OGIB) (overt and/or occult i.e. iron-deficiency anemia [IDA]), diarrhea, and/or abdominal pains. Therefore, direct visualization of the small bowel (SB) often becomes part of the necessary diagnostic workup in this patient group. Over more than a decade now, SB capsule endoscopy (SBCE) has gained a key role in the diagnostic approach of the SB [1]. Conversely, the use of SBCE and the characteristics of SB pathology in patients with chronic kidney disease (CKD) have been studied only in limited number of case series [2-7]. Furthermore, there is scarcity of data on the use of fecal calprotectin (FC) as selection tool for SBCE [1,8], even more so in patients with renal dysfunction who need to be prioritized to SBCE.

An increased prevalence of SB angiectasias has been reported in patients with CKD [5]. However, the exact impact of these findings, their endoscopic significance/severity grade, and furthermore their clinical impact is not well understood. Moreover, there is no known clinical indicator/marker when it comes to prioritizing these referrals.

This retrospective study, from a tertiary referral center, aimed to evaluate the use of SBCE in a cohort of patients with low estimated-glomerular filtration rate (e-GFR). Furthermore, we aimed to review the validity of FC in patients with impaired renal function who underwent SBCE.

Materials and methods

A review of the SBCE database of our hospital (a University hospital and tertiary referral center for capsule endoscopy for South East of Scotland, UK) was performed to identify patients with low e-GFR who had undergone a SBCE between March 2005 and August 2012.

The severity of kidney disease was classified in accordance with the Renal Association definitions [available from <http://www.renal.org/home#sthash.Nejfpmsh.dpbs>] [9]:

Stage 2 (e-GFR=60-89 mL/min/1.73m²): mildly reduced kidney function

Stage 3 (e-GFR=30-59 mL/min/1.73m²): moderately reduced kidney function

Stage 4 (e-GFR=15-29 mL/min/1.73m²): severely reduced kidney function

Stage 5 (e-GFR<15 mL/min/1.73m² or on hemodialysis): very severe, or end-stage kidney failure.

For the purpose of this study, advanced CKD was defined as stage 4 or 5 [2]. For each included patient, the e-GFR used was defined as the mean value of e-GFR readings over a prior 5-year period prior to the SBCE.

Data collection

Paper and electronic case notes were retrieved and reviewed. Age, gender, hemoglobin (Hb), mean corpuscular volume (MCV), platelets (Plt), ferritin, and FC levels were abstracted from electronic case notes (in each case, the result closest to the date of SBCE was selected). Certain medications that could have contributed to complications from SB pathology (i.e. aspirin, warfarin, angiotensin-converting enzyme inhibitors) were also abstracted, where the info was available. Important comorbidities and/or past medical history (diabetes, celiac disease, heart failure, heart and/or liver transplant, colectomy) and outcome were also noted for each patient.

Indications for SBCE

Indications for SBCE in our cohort were: OGIB; IDA; anemia (unspecified); known and/or suspected inflammatory bowel disease (IBD); diarrhea; celiac disease (CoD); and weight loss. Overt OGIB was defined according to the American Gastroenterological Association position statement as bleeding manifesting as melena and/or hematochesia and no obvious GI cause, following upper and lower GI tract endoscopy [10]. IDA was defined as iron deficiency with Hb <120 g/dL for

women and 135 g/dL for men (as per our laboratory reference range) [11,12]. In our center, we do not routinely perform SBCE for fecal occult blood tests.

Incomplete SBCE videos, i.e. videos where the capsule failed to pass into the cecum during the period of the recording, were not excluded from further analysis. The SBCE diagnostic yield (DY) for each CKD group was then calculated. SB angiectasias were classified according to the established classification for bleeding potential as P0 (non-pathological), P1 (low/indeterminate bleeding potential), or P2 (high bleeding potential) lesions [13].

SBCE procedure

SBCE was performed with the PillCam® SB1/SB2 (Given® Imaging Ltd, Yokneam, Israel) and the MiroCam® (IntroMedic Co, Seoul, South Korea) capsule endoscopes using the predefined for our unit regular procedure protocol, i.e., strict liquid diet the day prior to the test and SB purge (2 L polyethylene glycol; PEG, Moviprep®) with overnight fast. Hemodialysis patients were not given any PEG preparation, due to restriction of fluid intake; instead, they were placed on strict liquid diet the day before the procedure. In our center, capsule ingestion is performed with 40-100 mg of anti-foam (Simeticone, Infacol®) and 5 mg of liquid prokinetic (domperidone), unless in exceptional circumstances. The patients are allowed to drink clear fluids after 2 h and consume a light meal/snack after 4 h. All videos were re-checked (for the purpose of this study) by an expert capsule endoscopist (AK; experience >1,500 reviews).

Statistical analysis

Continuous data are expressed as mean ± SD (range) to one decimal place. Differences between groups were evaluated using chi-squared (χ^2) test for categorical variables and Student's two-sample *t*-test for continuous variables following a normal distribution or the Mann-Whitney *U*-test for those who failed the normality test. A *P* value <0.05 was considered statistically significant.

This study was conducted in accordance with UK research ethics guidelines. After review by the local ethics committee further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected endoscopy images, using data already obtained as part of regular clinical care [12].

Results

Demographics

A total of 69 patients with low eGFR (<60 mL/min/1.73 m²), who had undergone SBCE, were identified. 65 patients with moderate CKD i.e. stage 3 (20 males/45 females) were found; the rest (n=4) had severe CKD. Eleven patients were

also suffering from liver complications – (cirrhosis n=4, liver fibrosis n=2, autoimmune hepatitis n=1). 4/11 (36.3%) patients [eGFR 41±8.780 (29-49) mL/min/1.73m²] had undergone a liver transplant prior to having a SBCE: Hb levels 90.8±17.7 (76-114) g/L; MCV levels 80.3±6.9 (72-88) fL; Plt count 284.0±86.6 (201-389) × 10⁹/L; and ferritin 30.0±31.1 (8-52) µg/L. 2/4 (50.0%) of the liver transplant patients were referred for IDA with SBCE findings of non-specific fold edema (n=1) and normal (n=1). The remaining 2/4 (50%) liver transplant patients were referred for diarrhea, with SBCE findings of non-specific fold edema (n=1) and normal (n=1).

One female patient had undergone heart transplantation 11 years prior to having SBCE. A mean eGFR of 59 mL/min/1.73 m² placed her in the top end of stage 3 CKD. She was referred for IDA, her capsule reported non-specific fold edema.

Other important medical history and complications were found in 7/69 (10.1%) patients: colectomy for ulcerative colitis (n=4), adenocarcinoma of the kidney (n=2), and heart failure (n=1). Overall, there was no statistical difference with regard to demographics, medications used, prior comorbidities (apart from CKD), and prior history of transplant operations (Table 1).

CKD stage 3 subgroup (moderate CKD)

In this subgroup, the mean e-GFR (calculated from each patient's individual 5-year average value) was 49±7.9

Table 1 Patient demographics and clinical characteristics

| | Severe CKD | | Non-severe CKD | | P value |
|------------------------------|------------|---------|----------------|--|---------|
| | Stage 5 | Stage 4 | Stage 3 | | |
| Demographics | | | | | |
| No. of patients | 1 | 3 | 65 | | |
| Mean age (years)±SD | | | | | |
| Gender: M/F | 1/0 | 1/2 | 21/44 | | 0.596 |
| Medications | | | | | |
| Aspirin | 0 | 1 | 27 | | 0.642 |
| ACE-inhibitors | 0 | 2 | 29 | | 1.0 |
| Warfarin | 0 | 0 | 9 | | 1.0 |
| Co-morbidities | | | | | |
| Diabetes mellitus | 0 | 0 | 26 | | 0.289 |
| Celiac disease | 0 | 0 | 5 | | 1.0 |
| Heart failure | 0 | 0 | 12 | | 1.0 |
| Past surgical history | | | | | |
| Organ transplant | 0 | 0 | | | |
| Heart transplant | 0 | 0 | 1 | | 1.0 |
| Kidney transplant | 0 | 0 | 1 | | 1.0 |
| Liver transplant | 0 | 0 | 4 | | 1.0 |
| Colectomy (for UC) | 0 | 0 | 4 | | 1.0 |

CKD, chronic kidney disease; No, number; SD, standard deviation; M/F, males/females; ACE, angiotensin-converting enzyme; UC, ulcerative colitis

(30-59) mL/min/1.73 m². The most common indication for referral to SBCE was OGIB (78.5%; n=51); IDA (66.1%; n=43); and/or clearly defined overt-OGIB (12.3%; n=8). Fourteen (21.5%) patients were referred for indications other than OGIB (diarrhea, abdominal pain, and/or weight loss). The mean Hb level was: 100.8±19.8 g/L, MCV: 86.5±7.8 fl, Plt count: 244.9±105.8 × 10⁹/L, and ferritin: 116.0±337.0 µg/L.

In the OGIB group, 49.0% (n=25) had normal SBCE, while 33.3% (n=17) had angiectasias (P2 lesions: n=5), active bleeding (n=2), mucosal fold/villous edema (n=2), ileal erosions (n=1), adenocarcinoma (n=1), and inconclusive/non-available videos (n=3), (Table 2). The majority, 64.2% (n=9) of those referred for indication other than OGIB had normal SBCE. Angiectasias were uncommon in this group (n=1) (Table 2). Furthermore, there was no SBCE-related mortality.

CKD stage 4/5 subgroup (severe CKD)

4 patients had CKD stage 4 (n=3; 1M/2F) or 5 (n=1M); in CKD stage 4 the mean eGFR was 27±2.3 (25-29) mL/min/1.73m². The patient with CKD stage 5 was on dialysis and had an eGFR of <5 mL/min/1.73m². Two of the 3 (66.7%) patients with CKD stage 4 patients were referred for IDA and the other for diarrhea. The patient with CKD stage 5 was referred for normocytic anemia. In CKD stage 4 group, the mean Hb was: 85.3±21.2 g/L, MCV: 86.0±7.550 fl, Plt: 269.3±103.7×10⁹/L, ferritin: 251.0±333.5 µg/L. The patient in CKD group stage 5 had Hb: 95.0 g/L, MCV: 95.0 fl, Plt: 258.0×10⁹/L, and ferritin: 191 µg/L.

In the CKD stage 4 group, the SBCE showed angiectasias (ranging from P0 to P2, with only 1 P2 lesion); the other SBCE was normal. In the single patient on hemodialysis, SBCE encountered only jejunal angiectasias (P0).

Overall, there was no difference in the positive DY, i.e. sinister and non-sinister findings (P=0.43) between the 2 subgroups of patients with CKD.

Fecal calprotectin (FC)

12/65 (18.4%) patients (2 males/10 females) with CKD stage 3 [eGFR 51±8.019 (38-59) mL/min/1.73m²] had FC performed in the pre-referral workup. In this subgroup, mean Hb was 111.5±18.9 (76-136) g/L; MCV 91.2±6.3 (80-102) fL; Plt 249.1±94.8 (77-395) × 10⁹/L; and ferritin 61.3±86.1 (11-271) µg/L levels all lay within their respective reference ranges.

In this subgroup, no sinister pathology or SB inflammation was found; 5/12 (41.7%) SBCE were normal, 3/12 (25.0%) found angiectasias (3/3 grade P1), 1/12 (8.3%) found non-specific fold edema, and 3/12 (25.0%) capsules were incomplete.

Therefore, there was no statistically significant difference between the DY of patients who had FC measurement prior to their SBCE and the rest of the patients with CKD stage 3, P=0.25.

Other complications

Post-SBCE In CKD stage 3 group, 11/65 (16.9%) patients died (range: 0-34 months). Three deaths were attributed directly to the renal failure and 1 was reported to be due to a coronary event secondary to SB angiectasia bleeding. In CKD stage 4 group, 2/3 of the patients subsequently died (29 and 11 months post-SBCE, respectively); the cause of death was unrelated to the SBCE and/or any SB pathology.

Discussion

In the present study, we included 69 patients with moderate-severe CKD. In half of the cases (50.7%; n=35), the SBCE was normal/negative DY. In those with positive DY, the commonest SB finding was angiectasias (of any P-grade); 30.4% (n=21). The overall positive DY for this study (non-sinister pathology; angiectasia and active bleeding) was 23/69 (33.3%), which correlates with previous studies (Table 2). After excluding 6 SBCE, due to the fact that the videos were not available at the time of this study for review, the majority of patients (62/63; 98.4%) had a non-sinister SBCE diagnosis (Table 2). Findings of angiectasias were even lower in the subgroup of patients with high FC levels: DY of 25%, suggesting the limited use that FC has as an indicator of SB pathology, hence selection tool for SBCE, in patients with CKD.

Chalasan *et al* [14] suggest that there is a direct relation between prevalence of angiodysplasia and both the severity and duration of CKD. Indeed, in our study, clinically significant angiectasias i.e. P1/P2-grade, were found in

75% of patients with CKD stage 4 or 5 and angiectasias, as compared to 27.7% in patients of CKD stage 3, P<0.05. However, our CKD groups 4 and 5 consisted of just 4 patients. Conversely, Holleran *et al* [5] suggested that the development of SB angiodysplasia occurs early in the natural history of CKD, supporting the clinical validity of SBCE in this group of patients.

Only a limited number of studies looked into the use of diagnostic SBCE in patients with CKD. The majority of them showed a high DY with regards to SB pathology that could be contributing to OGIB e.g. angiectasias, active bleeding (Table 3). A study by Karagiannis *et al* [2] reported positive findings i.e. angiectasias in 47% of patients with CKD stage 4. Conversely, in the non-CKD patients the positive findings were only 17.6%. The number of these CKD patients totalled 17; 7 pre-dialysis, 4 on maintenance hemodialysis, 6 renal transplant recipients. Their results have been later confirmed by Sidhu *et al* [6]; these authors reported a DY of 33% (angiectasias) in patients with CKD (Table 3).

SB angiectasias can account for up to 40% of SB causes of OGIB [15]. However, up to 90% of them can spontaneously stop bleeding. This suggests that a finding of angiectasias in a patient with CKD does not necessarily mean it is the cause of unexplained anemia. This, combined with our 33.3% DY of angiectasias in patients with CKD, suggests that CE is not of especially significant use in diagnosing unexplained anemia in patients with CKD. There are of course other causes of anemia in patients with CKD: low erythropoietin production, uremic toxicity, low Plt production, poor GI absorption of iron etc. which should be fully investigated, perhaps before suggesting OGIB as the cause.

Our study was limited to patients with CKD, and did not compare the diagnostic yield of SBCE to a group of patients

Table 2 Table showing the DY per indication for patients with CKD stage 3, stage 4, and stage 5

| Indication | DY | | | | | Total (+) DY |
|--------------------|-------------------------|----------------------|-------------|-------------------|---------------------------------------|--------------|
| | Non-sinister pathology* | Sinister pathology** | Normal SBCE | Other findings*** | Inconclusive/not available for review | |
| CKD Stage 3 | | | | | | |
| IDA±OGIB | 19 | 1 | 25 | 3 | 3 | 23 |
| Anemia | 1 | 0 | 3 | 0 | 0 | 1 |
| Diarrhea | 0 | 0 | 3 | 1 | 2 | 3 |
| IBD | 0 | 0 | 2 | 0 | 0 | 0 |
| Celiac disease | 0 | 0 | 1 | 0 | 0 | 0 |
| Weight loss | 0 | 0 | 0 | 0 | 1 | 0 |
| CKD Stage 4 | | | | | | |
| IDA±OGIB | 2 | 0 | 0 | 0 | 0 | 2 |
| Diarrhea | 0 | 0 | 1 | 0 | 0 | 0 |
| CKD Stage 5 | | | | | | |
| Anemia | 1 | 0 | 0 | 0 | 0 | 1 |

CKD, chronic kidney disease; IDA, iron-deficiency anemia; OGIB, obscure gastrointestinal bleeding; IBD, inflammatory bowel disease; DY, diagnostic yield

*non-sinister pathology = angiectasias and/or active bleeding, **Sinister pathology = adenocarcinoma, ***Other findings = inflammatory-type of lesions i.e. mucosal fold edema and/or ileal erosions

Table 3 Comparison of DY of SBCE in patients with CKD between recent studies

| Authors, year, [ref] | Patients with CKD | Type of capsule | Indications | Severity of CKD | DY | DY criteria |
|------------------------------|-------------------|-------------------------|-------------|---|---|-------------------------------------|
| Docherty <i>et al</i> | 69 | PillCam [®] SB | OGIB | CKD 3, 4 and 5 | 33.3% | Angiectasias and/or active bleeding |
| Sidhu <i>et al</i> [5] | 26 | n/a | OGIB | - | 33% | Angiectasias |
| Karagiannis <i>et al</i> [2] | 17 | M2A [*] | OGIB | CKD 4 and 5 | 47% | Angiodysplasia |
| Sakai <i>et al</i> [4] | 44 | PillCam [®] SB | OGIB | This paper did not look specifically into patients with CKD | 20.2 % (This includes non CKD patients 148/242 – data for just CKD not available) | Vascular lesions |
| Ohmori <i>et al</i> [3] | 13 | PillCam [®] SB | OGIB | Hemodialysis | 61.5% | Vascular lesions |
| Kawamura <i>et al</i> [7] | 14 | PillCam [®] SB | OGIB | CKD stages 4 and 5 | 47.6% | Vascular lesions |

ref, reference; CKD, chronic kidney disease; IDA, iron-deficiency anemia; OGIB, obscure gastrointestinal bleeding; IBD, inflammatory bowel disease; DY, diagnostic yield

Summary Box

What is already known:

- Patients with poor renal function frequently present with obscure gastrointestinal bleeding
- Increased prevalence of small bowel (SB) angiectasias has been reported in patients with chronic kidney disease (CKD)
- There is only a limited number of studies/case series in the use of SB capsule endoscopy (SBCE) in patients with CKD
- There is scarcity of data on the use of fecal calprotectin (FC) as selection tool for SBCE

What the new findings are:

- SBCE endoscopy has a limited diagnostic yield in patients with CKD referred for investigation of unexplained anemia
- The most common finding is angiectasias, while sinister bowel pathology is rare
- Furthermore in CKD patients, FC measurement pre-SBCE is not associated with increased DY

without CKD. The difference in group sizes between CKD 3 and CKD 4/5, as mentioned above, presented difficulties in result comparisons and should be investigated with higher numbers.

In conclusion, SBCE endoscopy has limited DY in CKD patients referred for investigation of unexplained anemia. The most common finding is angiectasias, while sinister bowel pathology is rare. Furthermore, FC measurement pre-SBCE is not associated with increased DY.

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