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Original Article

Diagnostic role of capsule endoscopy in patients of obscure gastrointestinal bleeding after negative CT enterography

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Abstract

Background and Objectives: Computed tomographic enterography (CT-EG) has emerged a useful tool for the evaluation of small bowel in patients of obscure gastrointestinal bleeding (OGIB). However, CT-EG may be negative in about 50-60% of patients. We aimed to see the efficacy of capsule endoscopy (CE) in patients of OGIB, who had initial negative CT-EG. **Materials and Methods:** All consecutive patients of OGIB after initial hemodynamic stabilization were subjected to CT-EG. Those having negative CT-EG were further evaluated with CE. **Results:** Fifty-five patients of OGIB with mean standard deviation age, 52.7 (19.0), range 18-75 years, women 31/55 (56.4%) were subjected to CT-EG. Nine (17.6%) patients had positive findings on CT-EG, which included mass lesions in six, thickened wall of distal ileal loops, narrowing, and wall enhancement in two and jejunal wall thickening with wall hyperenhancement in one patient. Forty-two patients had negative CT-EG of which 25 underwent CE for further evaluation. CE detected positive findings in 11 of 25 (48%) patients which included vascular malformations in three, ulcers in seven, and fresh blood without identifiable source in one. The diagnostic yield of CE in overt OGIB was more compared to occult OGIB ((7/14, 50%) vs (4/11, 36.4%) $P = 0.2$) and was higher if performed within 2 weeks of active gastrointestinal (GI) bleed ($P = 0.08$). **Conclusions:** In conclusion, CE is an additional tool in the evaluation of obscure GI bleed, especially mucosal lesions which can be missed by CT-EG.

Key words

Capsule endoscopy, colonoscopy, computed tomographic enterography, obscure gastrointestinal bleed, upper gastrointestinal endoscopy

Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including upper GI endoscopy and colonoscopy. Overt OGIB is defined as visible GI bleeding (malena or hematochezia) and can be categorized further as active (evidence of ongoing bleeding) and inactive bleeding. OGIB is designated as occult when there is no evidence of gross bleeding, that is, unexplained iron deficiency anemia (IDA) suspected to be caused by GI blood loss.

About 5% of GI bleeding occurs between the ligament of Treitz and the ileocecal valve.[1] Vascular malformations of the small bowel account for 30-40% of OGIB in elderly population.[2] Nonsteroidal anti-inflammatory drug (NSAID) enteropathy and inflammatory bowel disease have been associated with erosions, ulcers, and strictures of the small bowel and may

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present as OGIB.[3,4] Small bowel tumors (gastrointestinal stromal tumors (GISTs), lymphomas, adenocarcinomas, and carcinoids) are most common cause of OGIB in patients of younger age group.[5] The other causes include Meckel's diverticulitis,[6] radiation enteropathy,[7] Dieulafoy's lesion,[8] hemosuccus pancreaticus,[9] and small bowel varices.[10]

Before evaluating small bowel, upper and lower GI endoscopies are repeated in patients with OGIB because of initial endoscopic miss rates in some patients.[11] Diagnostic methods for the evaluation of small bowel includes procedures like small-bowel follow-through and enteroclysis, angiography, scintigraphy, push enteroscopy, and intraoperative enteroscopy. However, all these techniques are either time consuming, operator dependent, require sedation, are relatively insensitive, or are highly invasive.[12] Newer technologies such as capsule endoscopy (CE), double balloon enteroscopy or CT enterography (CT-EG) have better access to small bowel and can provide improved care for patients with OGIB.[13]

CT-EG is a noninvasive imaging technique that uses neutral intraluminal and intravenous contrast to evaluate the small bowel and has been particularly useful in enhancement of the small bowel wall in inflammatory bowel disease. 64-slice CT systems has improved spatial and temporal resolution compared to 8- and 16-slice system and permits scanning of larger volumes of body in lesser amount of time without compromising on slice thickness. The role of CT-EG in the evaluation of OGIB is evolving.[14-17] The use of neutral enteric contrast agents such as water, polyethylene glycol (PEG), combined with the use of intravenous contrast optimizes luminal distention and depicts attenuation differences among the wall layers, the fluid-filled lumen and the adjacent mesenteric fat.[18,19] Initial experience with CT-EG reported successful identification of a bleeding source in 45% of patients with OGIB, including three lesions that were missed on CE.[14] In a study of 26 patients with massive GI bleeding, a multiple detector CT had an accuracy of 89% and positive predictive value of 95%.[20] The location of lesions corresponded exactly to that of active bleeding on angiograms in all patients. Despite above advantages negative CT-EG in patients of OGIB is quite high.

CE has been more efficient in picking up mucosal lesions compared to CT-EG. It is safe, noninvasive, well-accepted, and tolerated by the patient. This technique gives high resolution images of the whole small bowel, avoiding any sedation or radiation exposure. The capsules currently in use measure 26 × 11 mm, is propelled by peristalsis and has an imaging capacity of two frames per second over 8 h. A meta-analysis of 14 prospective studies showed a higher yield (56%) for clinically significant lesions with CE than with push enteroscopy (26%) or small bowel follow through (6%). In comparison with CT angiography (CTA) and standard angiography, CE detected more bleeding source lesions (72% with CE vs 24% with CTA and 56% with angiography).[21] High diagnostic yields (91.9%) for urgently performed CE (within 48 h after admission) in patients with mild to moderate acute overt OGIB suggest that early intervention with CE may enhance diagnostic effectiveness.

Despite the utility of CT-EG in establishing the cause of OGIB, negative rate of CT-EG in patients of OGIB is quite high. The aim of this study was to determine the diagnostic efficacy of CE in patients of OGIB who had initial negative CT-EG.

Materials and Methods

Subject population

This study was conducted in the Department of Gastroenterology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) along with Department of Radiodiagnosis from December 2010 to July 2012. Written informed consent was obtained from all patients who participated in this study. The study was approved by the institutional ethics and radiation safety committees. All patients of OGIB both overt and occult were included in this study after they were resuscitated, stabilized, and were not actively bleeding. These patients initially had CT-EG and those who had negative CT-EG were subjected to CE. The non-GI causes of IDA in patients with occult OGIB with negative fecal occult blood test (FOBT) were excluded with history, examination, and relevant investigations. Hematological indices and iron profile were used for diagnosis of IDA. Exclusion criteria included age <18 years, pregnancy, actively bleeding patient, unable to give consent, known allergy to iodized contrast material, renal insufficiency with creatinine >2, unable to swallow the capsule, and small bowel obstruction.

Study protocol

CT-EG was performed after overnight fast. A total of 2,000 ml of PEG electrolyte solution was given within 60 min prior to scanning, with first 1,500 ml ingested over first 15 min and two 250 ml aliquots consumed 25 and 15 min prior to scanning, respectively. A 100 ml of iohexol (300 mg/ml) (Omnipaque, Amershal GE healthcare, Princeton, NJ) was power-injected intravenously at a rate of 4 ml/s through antecubital catheter using dual head injector (Optivantage DH, Mallinckrodt) followed by saline flush. Scanning was performed on 64-channel multidetector row CT scanners (Siemens Sensation 64, Siemens Medical Solution, Forcheim, Germany) from diaphragm to the symphysis pubis. Images were acquired with a section thickness of 2.0-2.5 mm. Image evaluation was done by a consultant radiologist having more than 12 years' experience in interpreting CT studies of the GI tract.

CE was performed after overnight 8 h fast. Patients were on liquid diet for 24 h before the procedure and were given 1,000 ml of PEG solution on the night prior to procedure. Each patient ingested the capsule in sitting position (Mirocam Capsule Endoscopy, IntroMedic Co., Seoul, Korea). Patients were allowed to take clear liquids after 2 h and liquid diet after

4 h of procedure. When image acquisition was completed, the data from the recording device was downloaded to a computer workstation, where the images were processed and viewed by two consultant gastroenterologists independently and they were not aware of patient's initial CT-EG report. CE findings were classified as highly relevant (P2) or less relevant (P1 or P0) lesions according to the standard practice guidelines.[22] More than one P2 lesion was reported as positive, whereas, only a P1 lesion or no abnormality (P0) was reported as negative. The quality of the capsule endoscopic examination was evaluated by using a three-point scale of excellent, fair, or nondiagnostic, depending on the amount of feces or fluid that hindered visualization of the small-bowel mucosal surface.[23]

Statistical analysis

All statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 13.0 (SPSS Inc, Chicago, IL, USA). Data are presented as mean (standard deviation (SD)). Continuous and categorical values variables were analyzed by Fisher's exact test and Mann-Whitney U-test. A *P* value less than 0.05 was considered significant.

Results

Fifty-five patients of OGIB, mean (SD) age 52.7 (19.0), range (18-75 years), women 31/55 (56.4%) were subjected to CT-EG. Four patients had inadequate luminal distension to interpret CT-EG and were excluded. Nine (17.6%) patients had positive findings on CT-EG, which included six mass lesions in small bowel [Figure 1], two patients had thickened wall of distal ileal loops, narrowing, and wall enhancement and one patient had jejunal wall thickening with narrowing and wall hyperenhancement [Figure 2]. Patients with mass lesions were subjected to exploratory laprotomy and had mass lesions consistent with CT-EG findings. Histopathology of these lesions revealed GIST in four, duodenal adenocarcinoma in one, and duodenal carcinoid in one [Table 1]. Forty-two patients had negative CT-EG, of which 25 (59.5%) underwent CE for further evaluation. The baseline characteristics of patients who received CE are shown in Table 2.

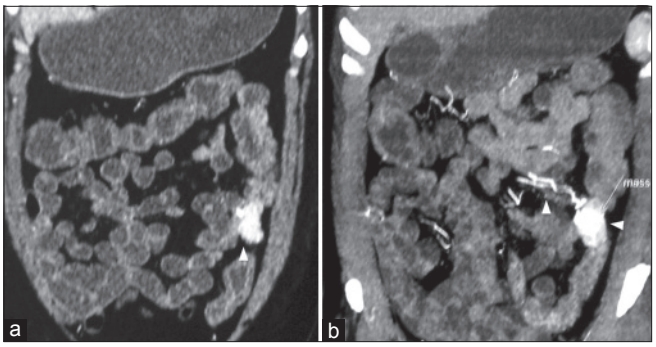

Figure 1: Computed tomography (CT) enterography in a patient of obscure gastrointestinal bleeding (OGIB) showing enhancing mass lesion in ileum with a feeding vessel

Results of CE

Among 25 patients who ingested capsule, one patient had image recording of only 2 h due to battery failure in capsule. In remaining 24, CE detected positive findings (P2 lesions) in 11 of 25 (44%) and P1 lesions in four patients. P2 lesions included vascular malformation in three [Figure 3], jejunal ulcers in one, ileal ulcers in five, blood in terminal ileum in one, and ileal ulcers with stricture in one [Table 3]. The diagnostic yield of CE in patients with overt OGIB was more compared to patients of occult OGIB ((7/14, 50%) vs (4/11, 36.4%) $P = 0.2$). Fourteen patients (56%) underwent CE within

Table 1: Outcome of CT-EG in patients of OGIB (*n*=51)

Diagnosis	Overt 27	Occult 24	Total 51
GIST	3	1	4
Duodenal adenocarcinoma	0	1	1
Duodenal carcinoid	1	0	1
Jejunal stricture	0	1	1
Ileal wall thinking with narrowing	0	2	2
Total (%)	4/27 (14.8)	5/24 (20.8)	9/51 (17.6)

GIST=Gastrointestinal stromal tumor, CT-EG=Computed tomographic enterography, OGIB=Obscure gastrointestinal bleed

Table 2: Baseline characteristics of patients of OGIB with negative CT-EG (*n*=25)

Age, mean (SD)	52.7 (19.0)
Range	18-75
Sex	
Women, *N* (%)	14/25 (56.4)
Overt OGIB, *N* (%)	14 (56)
No of bleeding episodes, mean (range)	3 (1-10)
Occult OGIB, *N* (%)	11 (44)
IDA with FOBT positive, *N* (%)	7 (63.6)
IDA with FOBT negative, *N* (%)	4 (36.4)
Duration of illness (weeks), mean (SD)	8.9 (9.1)
Range	(1-36)
Hemoglobin (g/dl), mean (SD),	6.8 (1.6)
Serum iron (µg/dl), mean (SD)	47 (7.5)
No of upper GI endoscopies, mean (range)	2 (1-5)
No of colonoscopies, mean (range)	1.24 (1-2)

OGIB=Obscure gastrointestinal bleed, CT-EG=Computed tomographic enterography, IDA=Iron deficiency anemia, SD=Standard deviation, FOBT=Fecal occult blood test

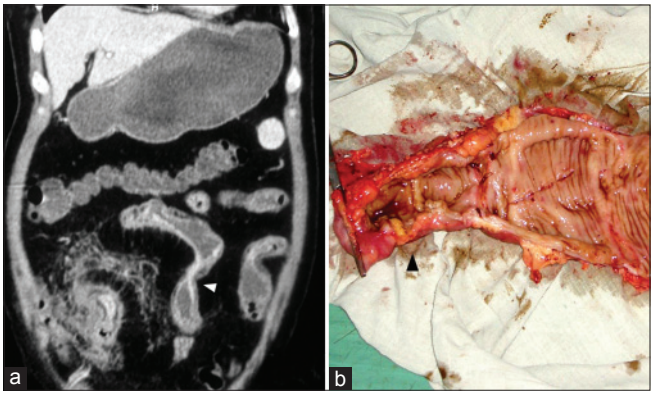

Figure 2: (a) CT-enterography showing jejunal stricture. (b) Surgical specimen showing stricture (adenocarcinoma)

2 weeks of last bleeding episode and 11 (44%) patients after 2 weeks. Seven of 14 patients had positive CE within 2 weeks, and four of 11 patients had positive CE after 2 weeks of last bleeding episode ($P = 0.08$) [Table 4].

The small bowel ulcers were the most common finding which occurred in seven of 11 patients [Figures 4a,5 and 6]. Two patients of ileal ulcers underwent double balloon enteroscopy and findings were similar with CE. These two patients had nonspecific ulcers on biopsy and received coagulation therapy. One patient with ileal ulcer had associated stricture with retention of capsule [Figure 4]. This patient underwent exploratory laparotomy, which revealed multiple ileal ulcers with strictures. Capsule was removed followed by resection anastomosis of diseased segment. Histopathology of removed segment revealed Crohn's disease. Two patients with nonspecific ulcers with oozing of blood [Figure 5] had history of nonsteroidal anti-inflammatory drug (NSAID) and aspirin intake. These two patients were kept under observation only and responded to iron therapy without further bleeding. Among three patients of vascular malformation, one patient was put on thalidomide for 2 months without any improvement in hemoglobin and thereafter, the drug was stopped. The other two patients were kept under observation, one patient did not develop further bleeding over a period of 10-12 months and other one patient developed recurrent GI bleed on follow-up and was transfusion dependent. One patient had blood in small bowel without any identifiable cause [Figure 7]. This patient was offered surgical intervention which he refused [Table 3].

Table 3: Patients of OGIB with positive capsule endoscopic findings (*N*=11)

Clinical features	Capsule endoscopy finding
Overt OGIB (malena)	Multiple ulcers seen from jejunum to terminal ileum
Abdominal pain, diarrhea, symptomatic IDA	Multiple ulcers in jejunum and ileum
Hypertension, coronary artery disease on aspirin. Symptomatic IDA	Multiple superficial ulcers in distal ileum
Overt OGIB (malena)	Diffuse flat ulcers in ileum with fresh blood at places
Overt OGIB (malena)	Multiple flat submucosal hemorrhages along blood vessels seen in ileum
Overt OGIB (hematochezia) abdominal pain	Multiple scattered large and small ulcers in ileum associated with stricture and divericulae
Symptomatic anemia (IDA)	Few flat submucosal hemorrhages seen in D1, D2 and multiple submucosal hemorrhages in jejunum
Overt OGIB (malena)	Multiple ileal ulcers, with oozing of blood from one of the ulcer
Overt OGIB (malena)	Fresh and old blood with clots seen in ileum
Overt OGIB (malena)	Two superficial ulcers in proximal ileum, one of ulcer oozing blood
Symptomatic anemia (IDA)	Multiple punctate hemorrhagic spots seen in ileum

OGIB=Obscure gastrointestinal bleed, IDA=Iron deficiency anemia

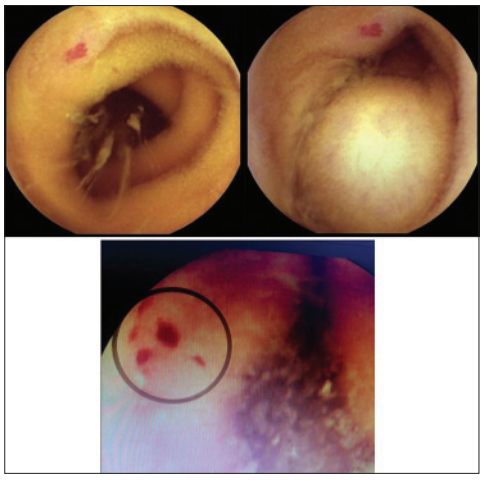

Figure 3: Capsule endoscopy in a patient of occult OGIB showing multiple hemorrhagic spots

Follow-up of CE negative patients

Thirteen patients (52%) had normal CT-EG and CE, out of which six patients had overt OGIB and seven patients had occult OGIB. Among six patients of overt OGIB, two patients underwent double balloon enteroscopy because of recurrent

Table 4: Diagnostic yield of capsule endoscopy in relation with time of bleed

Capsule endoscopy results (*N*)	Timing of bleed		Total
	Within 2 weeks	More than 2 weeks	
Positive	7	4	11
Negative	6	7	13
Total	14	11	24

P=0.08

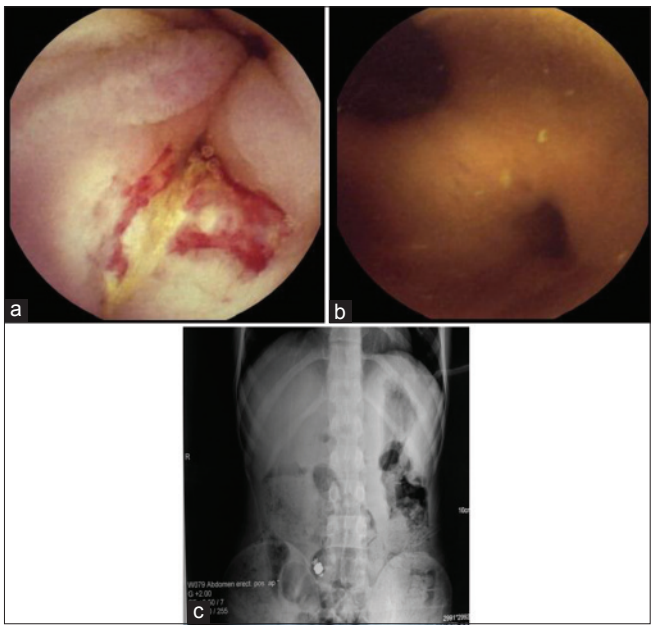

Figure 4: A 20-year-old male with abdominal pain, recurrent malena. Capsule endoscopy reveals: (a) ulcer in ileum (b) two diverticulae in ileum. (c) Abdominal X-ray showing capsule retention in ileum

bleeding; one of them had bleeding polyp in jejunum which was resected. The second patient had normal double balloon enteroscopy and is persistent with intermittent bleeding in the form of malena. The other four patients refused further investigations, among them one patient had no further bleed for >6 months and one patient had emergency laparotomy after 4 weeks of negative CE, due to major upper GI bleed (malena) with hypotension. This patient had intraoperative enteroscopy, which revealed a segment of jejunum with multiple areas of submucosal hemorrhages with oozing of blood. Resection anastomosis of jejunal segment was done. One patient was lost to follow-up and the fourth one is transfusion dependent. Among seven patients of occult OGIB with normal CE, two patients had IDA with positive FOBT and five patients had IDA with FOBT negative. Among these, three patients responded to iron therapy, two patients lost to follow-up, and two patients were persistent with anemia and were transfusion dependent [Table 5].

Figure 5: Capsule endoscopy in a patient of overt OGIB showing active bleeding from ileal ulcers

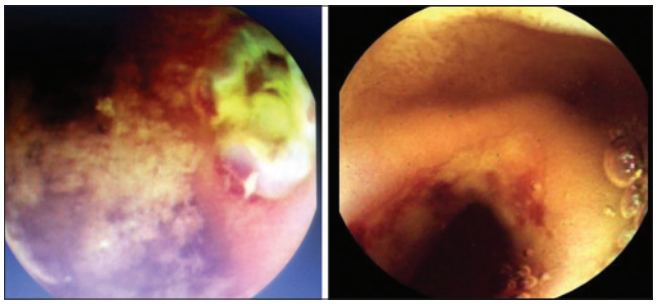

Figure 6: Capsule endoscopy showing multiple ileal ulcers

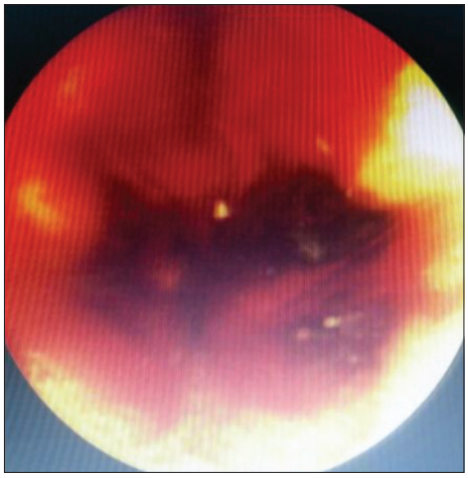

Figure 7: Capsule endoscopy showing active bleeding in small bowel

Discussion

The present study evaluated the diagnostic role of CE in patients of OGIB who had initial negative CT-EG. CT-EG revealed positive findings in 9/51 (17.6%) patients, which included GIST in three, duodenal adenocarcinoma in one, duodenal carcinoid in one, jejunal stricture in one, and ileal wall thickening with enhancement and narrowing in two patients [Table 1]. Forty-two (82.3%) patients had negative CT-EG, of which 25 underwent CE for further evaluation. CE revealed additional positive findings in 11/24 (45.8%) of patients. CE revealed mucosal lesions mainly ulcers (seven), vascular malformations (three), and active bleeding without identifiable cause in one patient which were missed in CT-EG, as CT-EG revealed mainly small bowel tumors and strictures.

Table 5: Follow-up and outcome in patients with normal CT-EG and CE (*N*=13)

Clinical finding	Other investigations	Follow-up
Symptomatic (IDA)	FOBT –ve, celiac profile –ve	Responded to iron therapy
Overt OGIB (malena)	-	No further malena >6 months
Overt OGIB (hematochezia)		No follow-up
Symptomatic (IDA)	FOBT +ve	No follow-up
Overt OGIB (malena)	-	Recurrent malena Transfusion dependent
Symptomatic (IDA)	FOBT –ve, celiac profile –ve	Responded to iron therapy
Overt OGIB (malena)	CTA, leakage of dye in jejunum	Peroperative enteroscopy multiple jejunal submucosal hemorrhages. Resection anastomosis of bleeding segment
Symptomatic (IDA)	FOBT –ve, celiac profile –ve	Responded to iron therapy
Overt OGIB (malena)	DBE: Bleeding polyp in jejunum	Surgical excision
Symptomatic (IDA)	FOBT –ve	Blood transfusion dependent
Overt OGIB (malena)	DBE: Normal	Persistent with intermittent malena
Symptomatic (IDA)	FOBT –ve, celiac profile –ive	No follow-up
Symptomatic (IDA)	FOBT +ve, celiac profile –ive	Blood transfusion dependent

FOBT=Fecal occult blood test, IDA=Iron deficiency anemia, OGIB=Obscure gastrointestinal bleed, DBE=Double balloon enteroscopy, CTA=Computed tomography angiography

CE allows direct visualization of the small bowel mucosa and has a high sensitivity for the detection of flat lesions such as ulcers, angiodysplasias, or arteriovenous malformations.

There is high incidence of negative CT-EG in patients of OGIB and miss rate of mucosal lesions is high. In a recent study from our center, 64-slice CT-EG in patients of OGIB picked up lesions in 46.9% of patients and the lesions were mainly small bowel tumors, while as negative CT-EG was seen in 53.1% of patients which needed further evaluation.[17] Heo *et al.*, recently evaluated the role of CE in patients with OGIB after negative CT-EG. They included 30 patients with OGIB who received CE after negative CT-EG. CE revealed a definitive diagnosis in 17 patients (57%), ulcer in nine patients (30%), active bleeding with no identifiable cause in five (17%), angiodysplasia in two (7%), and Dieulafoy's lesion in one (3%).[24] Rastogi *et al.*, found that diagnostic yield of CE was 42% in his study.[25]

In the present study, small bowel ulcers were the most common lesions followed by vascular malformations among patients who had positive CE. Vascular malformations occurred in the elderly patients. Previous studies have shown that angiodysplasia were the commonest finding and increasing age was the predisposing factor for high diagnostic yield of CE.[26,27] Vascular abnormalities account for 80% of OGIB, majority of which are angiodysplasias, whereas, small bowel tumors are found only in 1.6-2.4% of patients undergoing CE.[28,29] In this study, small bowel ulcers were the most common finding and occurred in the younger age group, among them two patients had early Crohn's disease which were missed by CT-EG. Some studies have shown that mucosal lesions like aphthoid ulcers, are not accurately visualized on CT-EG.[18] Nonsteroidal anti-inflammatory drug enteropathy and inflammatory bowel disease have been associated with erosions, ulcers, and strictures of the small bowel presenting as OGIB.[3,4]

In the present study, diagnostic yield of CE was higher in patients in whom CE was performed within 2 weeks of active GI bleed compared to patients who had CE after 2 weeks and also the yield was more in overt OGIB compared to occult OGIB, which is consistent with previous studies. Carey *et al.*, found that the diagnostic yield of CE was significantly higher when performed in patients with ongoing gastrointestinal bleeding than in those with more distant overt OGIB episodes.[30] The diagnostic yield of CE was significantly higher in patients with overt OGIB than those with occult OGIB.[24,29,31] In this study, one patient of small bowel Crohn's disease developed capsule retention [Figure 1]. This patient had multiple ileal ulcers with stricture. Previous one large study has shown that capsule retention rate in OGIB is 1.4%.[32]

Among patients with positive CE, eight patients received specific treatment in the form of surgery and coagulation therapy of bleeding ulcer on enteroscopy. Four patients received nonspecific treatment in the form of thalidomide, iron therapy, and blood transfusions. Accumulating evidence from multiple prospective clinical trials and two recent meta-analyses in patients with OGIB demonstrates the incremental value of CE in diagnosing etiologies of bleeding from the small bowel and the subsequent impact on patient management and outcomes.[12,33] In a previous study, CE detected bleeding sources in the small bowel in 57% of the patients who showed normal CT-EG findings. Lesions that were not detected by CT-EG included mucosal ulcers and angiodysplasias. In that study, two patients with small bowel Crohn's disease were missed by CT-EG.[24] In our study, CE detected bleeding source in 45.8% of patients who had normal CT-EG. The majority of lesions were small bowel ulcers and vascular malformations.

Both CT-EG and CE were negative in 13 (52%) patients; however, CT-EG and CE, both can be complimentary to each other. Huprich *et al.*, in 2011 compared CE with multiphase CT-EG in OGIB. The sensitivity of CT-EG was significantly greater than that of CE (88 vs 38%, $P = 0.008$), largely because it depicted more small bowel masses. On the basis of these findings, the addition of multiphase CT-EG should be included in patients with negative findings CE.[34]

Agarwal *et al.*, in 2011 studied the diagnostic yield of CT-EG in patients with OGIB and a nondiagnostic CE. CE was performed in 52 patients. CT-EG was then performed in 25 of the 48 patients without a definitive source of bleeding seen on CE. The diagnostic yield of CT-EG was 0% (0/11) in patients with occult bleeding versus 50% (7/14) in patients with overt bleeding ($P < 0.01$). The study revealed that in patients with a nondiagnostic CE, CT-EG is useful for detecting a source of GI bleeding in patients with overt, but not occult OGIB.[35]

The role of CT-EG in the evaluation of OGIB is evolving.[14-16] Huprich *et al.*, reported a high rate of positive findings by CT-EG in a small number of patients with OGIB.[14] In his study, CT-EG detected three small bowel lesions which were undetected by CE. CT-EG has an additional advantage of evaluating small bowel strictures, which cause retention of capsule and provide precise luminal and extraluminal findings that cannot be detected with CE.[14,23] Because of these advantages, some consider CT-EG as a complementary test to CE, especially in patients with OGIB. The main limitations of CT-EG include its lower yield than CE in detecting small bowel mucosal lesions, radiation exposure, relative poor distention of the small bowel, and limitations with intravenous iodinated contrast agent administration.[23,33,36]

There are several pitfalls and limitations in our study as the number of patients were small to generalize the results. CT-EG and CE was performed once bleeding was settled. There were five patients in whom the bowel preparation was poor, which hampered the visualization of mucosal details.

Conclusions

In conclusion this study reveals that a normal CT-EG does not guarantee that there is no bleeding source in the small bowel. CE

is better than CT-EG in detecting flat lesions like angiodysplasia and ulcers. Several factors including overt bleeding, ongoing active bleeding, and early performance of CE, likely increases sensitivity of CE in detecting causes of OGIB.

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