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Original Article

Capsule Endoscopy for Obscure Gastrointestinal Bleeding: A Single-Center Experience

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Abstract

Background: Capsule endoscopy (CE) has an established role in evaluating obscure gastrointestinal bleeding (OGIB). The aim was to know the diagnostic yield of CE and spectrum of OGIB. **Materials and Methods:** In this retrospective study, we evaluated all the patients with obscure gastrointestinal bleed using MiroCam capsule endoscope (IntroMedic, Seoul, Korea) between February 2014 and March 2018. Clinical data, ancillary investigations, and response to specific treatment were considered to confirm CE findings. **Results:** Out of 102 patients included in the study (mean age 54.5 ± 16.1 years, male: female ratio = 1.83:1) OGIB-overt and OGIB-occult was present in 46 and 56 patients, respectively. Diagnostic yield of CE was similar in both the groups (overt-37/46, 80.4% versus occult-37/56, 66.5%) ($P \geq 0.05$), although there was trend to find more lesions in overt group. Overall positive diagnostic yield was 72.5%. Lesions detected were vascular malformations in 21 (20.5%), nonsteroidal anti-inflammatory drug enteropathy in 13 (12.7%), small bowel ulcerations in 27 (26.4%), which were further divided into three subgroups (a) nonspecific ulcerations 11 (10.7%), (b) tubercular ulcer with/without stricture in 7 (6.8%) and (c) serpiginous ulcers and fissuring with cobble-stone appearance suggestive of Crohn's disease in 9 (8.8%), portal hypertensive enteropathy in 5 (4.9%), worm infestation (hookworms in 3, roundworms 1) in 4 (3.9%), and small bowel tumour in 1 (0.98%) patient. Overall, 56.7% patients were having definitive (P2) lesions (Saurin classification). Two patients had retention of capsule, but none developed intestinal obstruction. Capsule was removed with surgical intervention. **Conclusion:** CE has high diagnostic yield, relative safety and tolerability, and it is an important diagnostic tool for OGIB. Small bowel tuberculosis, Crohn's disease and Worm infestation continue to be commonly recognized causes of OGIB in developing countries like India.

Keywords: *Capsule endoscopy, obscure gastrointestinal bleeding, small bowel*

Introduction

Obscure gastrointestinal bleeding (OGIB) is characterized by continuous or recurrent bleeding originating in the GI tract after both upper and lower endoscopies yield no evidence of a source.[1] This can be further specified as obscure overt bleeding in which patients show clinical signs of active bleeding (e.g., hematochezia, hematemesis, and/or melena) or obscure occult bleeding which entails a patient testing positive on a fecal occult blood test or having refractory iron-deficient anemia.[1] Normally 0.5–1.5 ml of blood is lost from the GI tract daily, and this blood loss is not detectable by occult blood tests.[2] It takes more than 5 ml of daily blood loss in the GIT for the occult blood test to be positive. Patients with blood loss up to

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100 ml per day may have normally appearing stools.[3] Bleeding above this volume presents as visible GI bleed. Therefore, patients with daily GI blood loss between 5 and 100 ml would generally fall in the category of obscure occult GI bleed while those with blood loss of >100–150 ml per day have visible blood loss and are labeled as obscure overt GI bleeders.

Overall, OGIB makes up for 5% of all reported GI bleed cases, but continues to be a challenge because of delay in diagnosis and consequent morbidity and mortality.[4] Capsule endoscopy (CE) and device-assisted enteroscopy have established their position in the management algorithm for OGIB and have a significant impact on the outcome. CE has a higher diagnostic yield compared to other imaging techniques of the small bowel, including push enteroscopy and small bowel barium radiography and a comparable diagnostic yield as double balloon endoscopy.[5,6] The detection rate of CE for potential culprit lesion in OGIB ranges from 35% to 77%,[7] with performance dependent on various factors. Variables that have been associated with a higher detection rate includes, earlier WCE (within 1 week of bleeding), inpatient status, overt GI bleeding with tranfusion requirement, male sex, increasing age, use of warfarin, and liver comorbidity.[7] Obscure GI bleeding is now the primary and most important indication for CE. There is plethora of studies on CE in OGIB from western populations whereas studies from India are limited, with difference in etiological profile of OGIB. Hence, we planned this study to analyze the data of CE in patients with OGIB at our center to look for etiological spectrum and its diagnostic yield.

Materials and Methods

Study design

A single center, retrospective observational study, carried out at the tertiary care center from February 2014 to March 2018. The permission was granted from an Institutional Review Board to retrieve and analyze the data. GI bleeding was defined as passage of visible blood in vomitus or stools, or by positive results on stool occult blood tests. Data were collected on demographic profile, underlying disease, comorbidity, CE findings and follow-up of patients. The final diagnosis was made by taking the details of any further imaging, surgery, any specific treatment, and its response on outpatient department basis or telephonically.

Inclusion criteria

All patients without any contraindications and giving written consent for CE for evaluation of OGIB were selected. These included:

1. Patients with ongoing, obscure overt GI bleeding
2. Patients with a history of gastrointestinal bleeding with normal gastroduodenoscopy and ileocolonoscopy
3. Anemic patients with stool occult blood positive.

Exclusion criteria

1. Patients with clinical features suggestive of partial bowel obstruction or showing strictures on cross-sectional imaging
2. Failure to obtain consent
3. Hemodynamically unstable patients
4. Suboptimal study due to poor preparation or retention of capsule in the stomach.

Equipment

CE was carried out using Miro Cam capsules-Model no 1000 W and 1200 W (IntroMedic, Seoul, Korea). The patient swallowed this pill-shaped device weighing 3.25 ± 0.05 g with a size of 10.8×24.5 mm. The images were transmitted by radio frequency transmitter to a digital recorder worn on a belt through an eight-point sensor array pasted on specific locations on the abdomen. The capsule was capable of obtaining images at three frames per second, with a field of view of 170 degrees and a magnification of 102,400 pixels (320×320 pixels). Battery life was approximately 12 h, allowing a recording of at least 118,800 images during the study.

Capsule endoscopy procedure

CE was performed after overnight fasting and bowel preparation with 2 L of polyethylene glycol solution. Patients fasted during the first 4 h after ingestion of the capsule and then were allowed to take clear liquids. The recording device was returned in the evening for analysis, and the patients were sent home. Data were downloaded to a workstation (Miroview client, IntroMedic). The small bowel mucosal findings were recorded and analyzed later.

Follow-up

Patients were asked to note evacuation of the capsule, and those who were uncertain or suspected to have retained the capsule were followed by serial X-ray/fluoroscopic screening at weekly intervals for the next 2 weeks. Patients with confirmation of retained capsule were subjected to surgical removal. Patients were also followed up with medical therapy (such as treatment of Crohn's disease, institution of antitubercular therapy, or antihelminthic therapy), surgical therapy (for tumors or bleeding ulcers) or enteroscopic evaluation (ulcers, polyps, or bleeding angiodysplasia), depending on the CE results. Those with negative CE were followed up with expectant treatment.

Statistical analysis

Chi-squared test was used for categorical data, two-tailed $P < 0.05$ were considered significant. The statistical version SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for all frequency analysis and descriptive statistics.

Results

112 patients of OGIB admitted for evaluation during the study period were screened for eligibility. 10 patients were excluded from the study for various reasons as shown in [Figure 1]. 102 patients were eventually selected for final analysis. Out of the 102 patients with OGIB included in the study, 66 (65%) were male and 36 (35%) were female. The age ranged from 14 to 85 years with mean age 54.5 ± 16.1 years. For comparison patients were divided into two groups on the basis of age (>60 vs. ≤60 years). There was no statistical difference between two groups for obscure or overt etiology of GI Bleed on the basis of age and sex [Table 1].

Indication for capsule endoscopy

Although GI bleed was present in all the patients, 10 patients in occult group also had-chronic diarrhea (2) and abdominal pain (8) [Table 1].

Capsule endoscopy findings

Lesions were detected in 74 of 102 (72.5%) patients. Vascular malformations were identified in 21 (20.5%), nonsteroidal anti-inflammatory drug enteropathy (NSAID) enteropathy in 13 (12.7%), small bowel ulcerations in 27 (26.4%), which were further divided into three subgroups (a) nonspecific ulcerations 11 (10.7%), (b) tubercular ulcer with/without stricture in 7 (6.8%) and (c) serpiginous ulcers and fissuring with cobble-stone appearance suggestive of Crohn's disease in 9 (8.8%), Portal hypertensive enteropathy in 5 (4.9%), Worm infestation (hookworms in 3, roundworms 1) in 4 (3.9%), Small bowel tumor and Duodenal ulcer in 1 (0.98%) patient each. The small bowel was found to be normal on CE in 28 (27.4%) patients. The overall distribution of lesions is shown in [Table 2, Figures 2 and 3]. On comparison between overt and occult obscure GI Bleed causes, only vascular malformations were found to be significantly higher in the overt group ($P < 0.05$).

CE findings were also classified according to their clinical significance, in line with Saurin classification, as P0: Low probability; P1: Intermediate probability; P2: High probability.[8] P0 lesions were defined as those with no potential for bleeding including visible mucosal veins, diverticula without the presence of blood,

Table 1: Comparison of occult versus overt gastrointestinal bleed groups on the basis of demographic variables and indications for capsule endoscopy

	Occult (*n*=56)	Overt (*n*=46)	Total	*P*
Age (years)				
≤60	31 (55.35)	27 (5.87)	58 (56.86)	>0.05
>60	25 (44.64)	19 (41.30)	44 (43.14)	
Sex				
Male	36 (64.28)	30 (65.22)	66 (64.71)	>0.05
Female	20 (35.71)	16 (34.78)	36 (35.29)	
Indication for capsule endoscopy, *n* (%)				
GI bleed	46 (82.14)	46 (100)	92 (90.2)	NA
Abdominal pain	8 (14.29)	0	8 (7.84)	
Chronic diarrhea	2 (3.57)	0	2 (1.96)	

GI=Gastrointestinal, NA=Not available

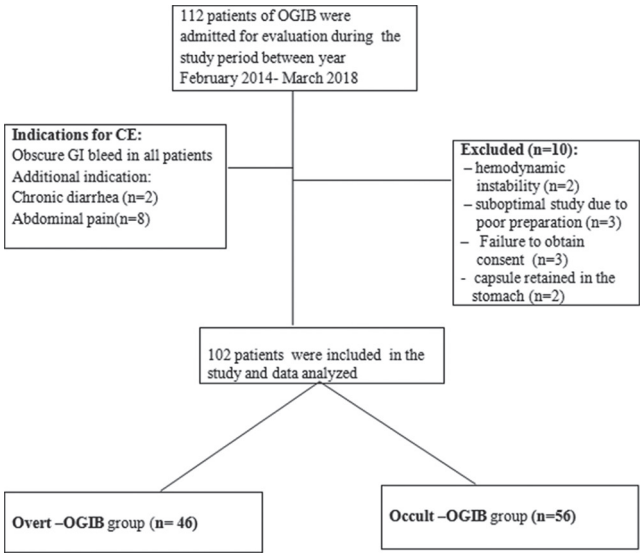

Figure 1: Enrollment of patients of obscure gastrointestinal bleed for capsule endoscopy

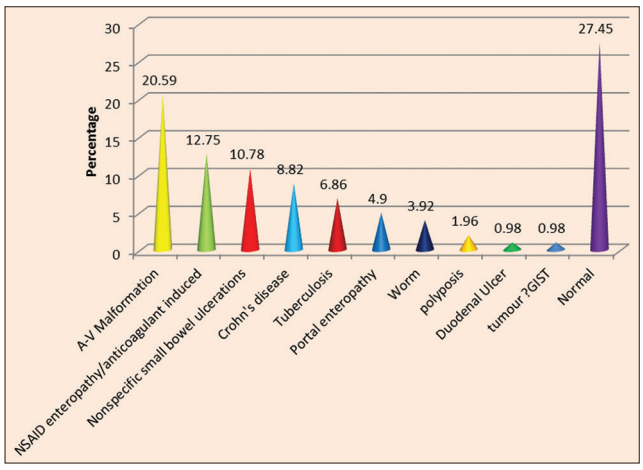

Figure 2: Classification of findings on capsule endoscopy in patients with obscure gastrointestinal bleeding

Table 2: Final diagnosis based on capsule endoscopy findings

Finding	Occult	Overt	χ^2	df	*P*	Significance
Vascular malformations	7 (21.43)	14 (30.43)	4.970	1	<0.05	S
NSAID enteropathy	5 (8.93)	8 (17.39)	1.630	1	>0.05	NS
Nonspecific small bowel ulcerations	5 (8.93)	6 (13.04)	0.008	1	>0.05	NS
Small bowel tuberculosis	6 (10.71)	1 (2.17)	1.666	1	>0.05	NS
Worms	2 (3.57)	2 (4.35)	0.076	1	>0.05	NS
Portal hypertensive enteropathy	2 (3.57)	3 (6.52)	0.073	1	>0.05	NS
Polyposis syndrome	1 (1.79)	1 (2.17)	0.333	1	>0.05	NS
Crohns disease	9 (16.07)	0 (0.00)	-			
Small bowel tumour	0 (0.00)	1 (2.17)	-			
Duodenal ulcer	0 (0.00)	1 (2.17)	-			
Normal study	19 (33.93)	9 (19.56)	2.620	1	>0.05	NS

NSAID=Nonsteroidal anti-inflammatory drugs, NS=Not significant, S=Significant

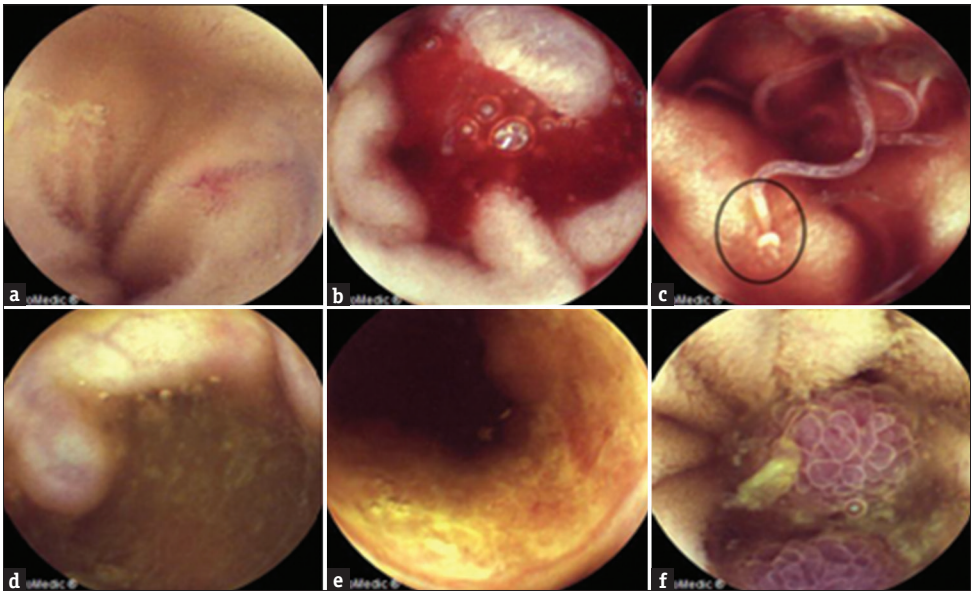

Figure 3: Capsule endoscopy images showing (a) vascular malformation (b) submucosal tumour with active bleed? gastrointestinal stromal tumor (c) hookworm sucking blood (d) Ectopic varix in a patient with eradiacted esopahageal varix (e) small bowel stricture? Tubercular (f) multiple polyps in proximal jejunum

nodules without mucosal break, P1 lesions were those regarded as having uncertain hemorrhagic potential, such as red spots on the intestinal mucosa, or small or isolated erosions and P2 lesions were those considered to have a high potential for bleeding, such as typical angioectasia, large ulcerations, tumors or varices. In our study, proportion of patients with lesions of each category in the overt–OGIB group were P2-46%, P1-35%, P0-19%, whereas in occult group, this was P2-37%, P1-28%, P0-34% respectively [Figure 4]. There was no statistically significant difference for P2 lesions between the two groups ($P < 0.05$). The lesions in P2 group included vascular malformations with active bleeding or stigmata of recent hemorrhage (10), NSAID induced ulceration (4), small bowel ulcers typical of tuberculosis (1), small bowel tumour (1), polyps (1), hookworm actively sucking blood (2), portal hypertensive enteropathy with active oozing of blood (1) and duodenal ulcer (1) in overt group whereas in occult group, P2 lesions were vascular malformations (4), NSAID enteropathy (3), small bowel ulcer of tubercular (4) and Crohn's etiology (7), polyps (1), hookworm (1) and portal hypertensive enteropathy (1). In both the groups, P1 lesions included nonspecific small bowel ulcers and erosions, doubtful vascular malformations, portal hypertensive enteropathy and worms (roundworm).

Patients with vascular malformations were managed with hematemesis and hormonal therapy, one patient with recurrent massive GI bleed was sent to other center and underwent Argon plasma coagulation and improved. NSAID enteropathy was defined in clinical context, when history of ongoing or recent (within 2 weeks history of NSAID/aspirin consumption)

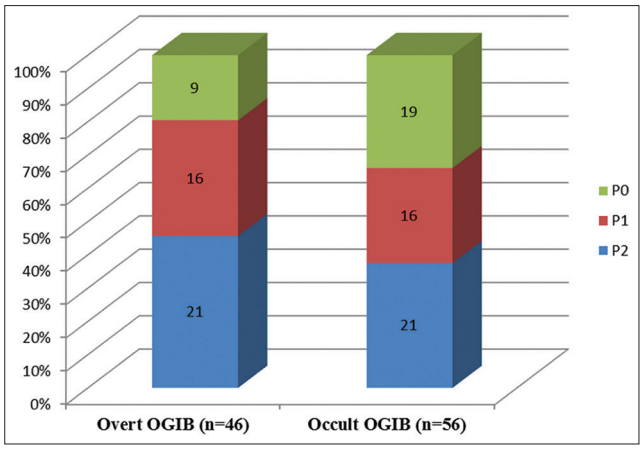

Figure 4: Number of patients in both groups as per Saurin classification of capsule endoscopy findings

was available. NSAIDS can cause multiple erosions, ulcerations, and strictures characteristically "Diaphragm like" strictures[9] as seen in our patients. All the patients improved on stopping antiplatelets. Patients with small bowel ulcerations were categorized on the basis of clinical, CE, and cross-sectional imaging findings and response to treatment into three groups as described previously. Nonspecific small bowel ulcerations group was managed with iron supplements and improved whereas patients in tubercular and crohn's group improved on specific treatment. Portal hypertensive enteropathy was defined by mucosal edema, congested rounded blunt villi giving a classic "herring-roe" appearance, loss of vascularization, friability, hyperemia, flat red spots, angiodysplasia such as lesions, pigmented black-brown spots, mucosal granularity, reticulated mosaic-like pattern mucosa, protruding red bumps, inflammatory polyps, and varices as described in literature.[10] These patients were managed with Beta blockers and supportive treatment. Worm infestation alone was the cause of GI bleeding in two patients. Hookworms were seen, some actively sucking the blood [Figure 3]. All of them responded to anti-helminthic therapy. Small bowel tumour was seen in only one patient, who underwent laparotomy and resection of tumour, histopathology was suggestive of gastrointestinal stromal tumor. Multiple polyps were seen in two patients, both underwent single balloon enteroscopy and polyp removal, which came out as hamartomatous polyps on histology and were diagnosed as peutz jeghers syndrome. One patient was having Duodenal Ulcer which was missed on pre CE gastroscopy. The diagnostic yield of CE in OGIB-occult and OGIB-overt groups were 66.0% and 80.4%, respectively, with no statistically significant difference between two groups ($P > 0.05$).

All the 28 patients with negative capsule endoscopy were also followed. One young patient with recurrent overt GI bleed underwent laparotomy for Meckel's diverticulum diagnosed on Meckel's scan. Two elderly patients with recurrent overt GI bleed were advised for laparotomy, but refused and died on follow up. Of the remaining 25 patients in this group, only 16 patients were available for a follow-up of 1 year, and none had any significant bleeding.

Capsule retention

Capsule retention was noted in two of 102 patients (1.96%). Both patients had strictures in the small bowel due to chronic NSAID use. These patients underwent surgery and capsule was retrieved and were found to have typical diaphragm-like strictures. Both patients are alive and asymptomatic.

Discussion

Since the introduction of first video capsule endoscope in 2001 by Iddan[11] as a new tool for the investigation of the small bowel, CE has revolutionized the field of small-bowel imaging and has brought about a paradigm shift in the diagnosis and management of OGIB. The consensus statement from the 2005 international conference on CE recommends CE after initial negative esophagogastroduodenoscopy and colonoscopy in patients with obscure gastrointestinal bleed.[12] Current study has an overall positive diagnostic yield of 72.5%, which is fairly good and is in accordance with published literature as described in a review by Wang *et al*. where the detection rate of WCE for potential culprit lesion in OGIB ranges from 35% to 77%,[7] with performance dependent on various factors. The diagnostic yield reported in previous Indian studies were variable ranging from 52% to 74% [Table 3].[13-18] This could be explained by well-established fact that patient selection and timing of the CE procedure largely influence the yield.

Etiology for OGIB as detected by CE has varied from study to study. Vascular malformations or angiodysplasia were the most common finding in the present study. Ghoshal *et al*. also had vascular malformations as the most common finding in their study.[15] Comparable results were seen in the studies done by Tong *et al*. and Zhang *et al*., who in their review had proposed angiodysplasia as the most common cause of OGIB in patients age >65 years.[19,20] Goenka *et al*. had reported ulcers as the most common finding in their study.[14] In our study also, small bowel ulcers as a common group is the most common etiology, but as we have segregated the patients with small bowel ulcers etiology as nonspecific and specific etiology defined as tubercular, Crohn's disease, and NSAID group, our percentage of small

Table 3: Comparison of Indian studies on diagnostic yield and capsule endoscopy findings

	Total patients (*n*)	Overt (*n*)	Occult (*n*)	Diagnostic yield overall (%)	Diagnostic yield overt (%)	Diagnostic yield occult (%)	Most frequent lesionsidentified (%)
PVJ Sriram *et al*., 2004	24	_	_	66.6	_	_	Angioectasiae, leiomyomata and parasitic infestation
Gupta *et al*., 2006	154	74	80	52	77	27	NSAID induced lesions (15), angiodysplasias (14), aphthous ulcers (12)
Goenka MK *et al*., 2011	385	_	_	74	87	59	Small bowel ulcer (70)– Crohn's disease, tuberculosis, NSAIDS induced, worms and nonspecific Tumours (21.6) Angiodysplasia (8)
UC Ghoshal *et al*., 2011	86	64	22	75	81.8	74.4	Vascular malformations (37.5) Tumors (18.8) Strictures (23.4) Ulcers (7.8) Hookworm (7.8)
JS Sodhi *et al*., 2013	25	14	11	48	50	36	Vascular malformation (27) Ulcers (64)
Gaikwad NR *et al*., 2017	21	_	_	61.9	_	_	Aphthous ulcer (19.04) Telangiectasia (14.28) NSAID enteropathy (4.7)
Present study, 2018	102	46	56	72.5	80.4	66.5	Vascular malformations (20) NSAID enteropathy (12.7) Small bowel ulcers (26.4) Worms (3.9)

NSAID=Nonsteroidal anti-inflammatory drugs

bowel ulceration as etiology of OGIB individually is lower. NSAID enteropathy induced GI bleed constituted the second most common etiology in our study. The blood loss can be acute or more commonly chronic as occult gastrointestinal blood loss.[9] Worm infestation, particularly Hookworm, detected on CE in our series is a unique cause of OGIB in tropical countries as previously highlighted by various case reports, case series and large studies from India.[13-16,21,22] Small bowel tuberculosis was seen in seven patients in our series. CE findings were comparable to previous series described.[23,24] Response to antitubercular treatment served as a surrogate marker to confirm the diagnosis of small bowel tuberculosis. We also found changes of portal hypertension enteropathy in five patients of chronic liver disease with persistent anemia and evidence of chronic blood loss, despite eradication of the esophageal varices and no other bleeding source on upper and lower gastrointestinal endoscopy, with findings similar to those described in literature.[10] CE currently plays an important role in Crohn's disease (CD) evaluation with particular emphasis on early diagnosis of small bowel crohn's, assessment of extent of disease in diagnosed Crohn's and in monitoring for mucosal healing. In our series, nine patients were diagnosed Crohn's disease on the basis of CE findings,[25] computed tomography (CT) enterography, exclusion of tuberculosis and response to treatment.

The yield of CE in our study, for detecting lesions in patients with OGIB-overt and OGIB-occult group was similar, although there was trend to find more lesions in

overt group. A study by Benevante *et al*. showed equal yield in both groups,[26] whereas other studies showed that detection rates of bleeding lesions was higher in patients with OGIB-overt than OGIB-occult.[16,27,28] In our study, overall, 56.7% patients were having definitive (P2) lesions. Goenka *et al*. in their study reported 58% definite lesions that could unequivocally explain OGIB. Ghoshal *et al*. confirmed that the CE findings by surgery or response to treatment and calculated true positive findings in 39 patients out of total 64 lesions identified, which transforms the yield of CE as 61% for definitive lesions. Similarly, Macdonald *et al*.[29] in their study also showed the overall diagnostic yield of 57% for P2 lesions although, the most commonly found lesion was angiodysplasia (79%).

Capsule retention is the main potential adverse event of CE, which is defined as a capsule endoscope remaining in the digestive tract for a minimum of 2 weeks or one that has required directed therapy to aid its passage. A systematic review by Rezapour *et al*. have described the CE retention rates of approximately 2% of patients undergoing evaluation for small-bowel bleeding and is most likely due to small-bowel strictures. Retention rates in patients with suspected or known IBD were approximately 4% and 8% respectively.[30] These rates are decreased by half in those studies that used either a patency capsule or CT enterography to assess patency before performing CE. In our study, capsule retention rate was 1.96%. We did not use the patency capsule in any of the patient because of resource constraints, but both the patients with capsule retention were not having any symptoms suggestive of intestinal obstruction nor do have any suggestive findings on cross-sectional imaging. Both the patients underwent surgery and were found to have NSAID induced strictures.

Limitations of our study were its retrospective nature and inability to have conclusive histopathological or tissue diagnosis for most of the patients. Second, the study did not offer long-term follow-up of the patients, and hence, made it impossible to draw a strong conclusion on long-term outcomes of patients with recurrence of OGIB in the absence of definitive treatment and patients with P1 and P0 lesions, respectively. Hence, larger prospective studies are needed in the future.

In summary, high diagnostic yield, relative safety, and tolerability have established CE as an important diagnostic tool for OGIB. In fact, recently, it has been proposed that the term obscure gastrointestinal bleed, should only be used if a source of bleeding is not identified after a thorough examination of the entire gastrointestinal tract, including the small bowel. Most cases of what was previously referred to as obscure bleeding were more correctly categorized as suspected small bowel bleeding.[31] Hence, negative CE may be the defining criteria for OGIB in the future. This study also highlights the fact that small bowel tuberculosis, Crohn's disease and worm infestation are commonly recognized causes of OGIB in developing countries like India as described in the previous studies.

Conclusion

Capsule endoscopy is an excellent tool in evaluation of obscure gastrointestinal bleeding with relative safety and high diagnostic yield which help in guiding therapeutic management.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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