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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (19): Capsule endoscopy

Capsule endoscopy in pediatrics: A 10-years journey

Salvatore Oliva, Stanley A Cohen, Giovanni Di Nardo, Gianfranco Gualdi, Salvatore Cucchiara, Emanuele Casciani

Salvatore Oliva, Giovanni Di Nardo, Salvatore Cucchiara, Department of Pediatrics, Pediatric Gastroenterology Unit, Sapienza University of Rome, 00161 Rome, Italy
Gianfranco Gualdi, Emanuele Casciani, Radiology DEA, Sapienza University of Rome, University Hospital Umberto I, 00161 Rome, Italy
Stanley A Cohen, Children's Center for Digestive Health Care, Atlanta, GA 30342, United States
Author contributions: All authors contributed equally to this paper.
Correspondence to: Emanuele Casciani, MD, Radiology DEA, Sapienza University of Rome, University Hospital Umberto I, Viale Regina Elena 324, 00161 Rome, Italy. emanuelecasciani@gmail.com
Telephone: +39-64-9979537 Fax: +39-64-9979537
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Abstract

Video capsule endoscopy (CE) for evaluation the esophagus (ECE), small bowel (SBCE) and the colon (CCE) is particularly useful in pediatrics, because this imaging modality does not require ionizing radiation, deep sedation or general anesthesia. The risk of capsule retention appears to be dependent on indication rather than age and parallels the adult experience by indication, making SBCE a relatively safe procedure with a significant diagnostic yield. The newest indication, assessment of mucosal change, greatly enhances and expands its potential benefit. The diagnostic role of CE extends beyond the SB. The use of ECE also may enhance our knowledge of esophageal disease and assist patient care. Colon CCE is a novel minimally invasive and painless endoscopic technique allowing exploration of the colon without need for sedation, rectal intubation and gas insufflation. The limited data on ECE and CCE in pediatrics does not yet allow the same conclusions regarding efficacy; however, both appear to provide safe methods to assess and monitor mucosal change in their respective areas with little discomfort. Moreover, although experience has been limited, the patency capsule may help lessen the potential of capsule retention; and newly researched protocols for bowel cleaning may further enhance CE's diagnostic yield. However, further research is needed to optimize the use of the various CE procedures in pediatric populations.

Key words: Capsule endoscopy; Children; Small bowel; Pediatric endoscopy

Core tip: Recent investigations using capsule endoscopy as a tool to monitor mucosal change with therapy and to improve bowel cleaning (which potentially will increase the diagnostic yield) and new capsules to evaluate the esophagus and colon present an enhanced value to be gained from capsule endoscopy, 10 years after investigations began in pediatrics.

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INTRODUCTION

Since 2001, capsule endoscopy (CE) has been used to evaluate small bowel pathology in adults. In patients of 10 to 18 years of age, these evaluations began in January 2004[1]. In 2009, CE was also approved by United States Food and Drug Administration (FDA) for use in children 2 years of age and older[2]. As a result, the use of CE has expanded in the pediatric population over the past decade, largely because of the possibility of avoiding ionizing radiation, deep sedation and general anesthesia. That success has prompted CE evaluations of the esophagus and colon as well while broader indications and applica-

Table 1 Clinical indications, outcomes and adverse events by different age groups

	Adult	Pediatric	< 8 yr
Indications (%)			
OGIB + IDA	66	15	36
CD/UC/IC	10	63	24
Abdominal pain	11	10	14
Polyps/Neoplasms	3	8	-
Other	10	4	25
Outcomes (% positive findings for different indications)			
OGIB + IDA	61	42	-
CD/UC/IC	55	65	-
Abdominal pain	23	43	-
Polyps/Neoplasms	56	75	-
Overall	59	61	67
Adverse events (%)			
Capsule retention	1.4	2.6	0.5
Incomplete examinations	16	13	7
Other	1.1	0.9	-

CD: Crohn's disease; IDA: Iron deficiency anemia; OGIB: Obscure gastrointestinal bleeding; IC: Indeterminant colitis; UC: Ulcerative colitis.

tions of CE are being defined in the diagnosis and monitoring of gastrointestinal disease.

SMALL BOWEL CAPSULE ENDOSCOPY

Because the small intestine was often considered as the mysterious "black box" of the GI tract, small bowel capsule endoscopy (SBCE) has become particularly valuable for pediatric patients to achieve a definite diagnosis in cases with small bowel pathologies [(*i.e.,* Crohn's disease (CD)] or obscure gastrointestinal bleeding) such that the small bowel is no longer the frontier that it had been in the past[3].

Indications

The American Society for Gastrointestinal Endoscopy developed indications for SBCE[4]. However, the relative frequency of indications in compiled pediatric reports differs from that in data regarding adults. In adults, 66% of CEs have been for obscure gastrointestinal bleeding (OGIB) including iron deficiency anemia (IDA); 11% for clinical symptoms only (*e.g.,* pain, diarrhea, and weight loss without OGIB); 10% for CD; with the balance (13%) for other indications[5-25]. In pediatric patients, 60% of CE have been for CD, 15% for OGIB, 10% for abdominal pain/diarrhea, and 8% for polyposis[15,16]. More than half of the procedures for IBD indications are related to evaluation of CD and colitis, with 44% due to the suspicion of CD, 16% related to evaluation of known CD, 2% to differentiate indeterminate colitis (IC), and 1% to further evaluate ulcerative colitis (UC). Abdominal pain and diarrhea account for another 10% of the procedures and might be considered as evaluations for the same indications.

Even within the pediatric population, these clinical indications are age-stratified (Table 1). In a review of 83 procedures in children aged 1.5-7.9 years (when CD is less prevalent), the most common indication for CE was OGIB, accounting for 30 (36%) procedures, with positive yields in 16 (53%)[21]. Suspicion of CD accounted for 20 (24%) procedures, with positive findings in 11 (55%). Abdominal pain accounted for another 12 procedures (14%), and CD was the indication in 3 patients. CD was found in 14 (31%) of the patients where a positive diagnosis was made. Investigation of malabsorption and protein loss required 12 and 9 procedures (14% and 11%), respectively, with positive findings in 6 each. In contrast, OGIB in older children (age 10-18 years) accounted for only 13%-24% of all indications[5,9,11,17,19,23].

Additionally, SBCE is being used to identify eosinophilic enteropathy (with areas of erythematous, denuded mucosa)[9]; an ulcerative inflammatory enteropathy in cystic fibrosis[26] graft-vs-host disease[8]; monitoring medical therapy in CD[5-27]; and to evaluate the graft's integrity after small bowel transplantion[7,8].

Preparation

The inability to establish the exact location of the capsule in the small intestine, and the inability to flushing or suction fluids make adequate bowel cleaning of particular importance for SBCE. Debris, biliary secretion, bubbles and blood, especially in the distal small bowel, and failure of the capsule to reach the cecum have the potential to limit the diagnostic yield[28].

Since cleaning the small intestine prior to examination may improve the diagnostic yield, CE-preparation regimens-mainly using the same products adopted for colonoscopy preparation-have been proposed[29]. But the optimal preparation regimen is yet to be established[30]. A clear liquid diet the evening before CE and an overnight fast appears to be associated with poor visibility of the terminal ileum in the majority of patients[30]. Since simethicone seems to improve mucosal visualization and tolerability by reducing air bubbles, flammable gas (namely, hydrogen) and abdominal discomfort[31], a combination of simethicone and polyethylene glycol (PEG) has frequently been promulgated as an effective means to increase the visibility of the small intestine (SB)[4,32-35].

The only pediatric study to date prospectively evaluated 198 patients with five different preparation regimens[35]. The mucosal visibility of the SB was assessed at five equal time points. After preparation with PEG and simethicone, discomfort was lessened and mucosal visualization improved significantly in the distal ileum, which is the portion most often affected by debris. However, the overall diagnostic yield was not affected except in the last section of SB.

The least amount of PEG solution tested, 1.75 g/25 mL per kg (up to 1 Lt) of PEG solution (70 g/1000 mL) the night before the procedure plus 20 mL (376 mg) oral simethicone 30 min before capsule ingestion appears to be the preparation of choice for SBCE in children. No significant differences were found regarding gastric and small-intestinal transit times or in the proportion of patients in whom the cecum was not visualized. However, intestinal transit is much faster in children than adults

and therefore bowel preparation might not impact intestinal transit time in the pediatric age group compared to adults.

Patient outcomes

A meta-analysis[5] and additional reports from the pediatric literature[6,7], comprised 995 patients who underwent 1013 CE procedures with positive findings in 511 (61.4%; 95%CI: 52.7%-69.7%). Studies were complete (*i.e.,* the capsule reached or passed the ileocecal valve by the end of the recording period) in 846 procedures. (86.0%; 95%CI: 81.6%-89.9%)[5-7]. In the studies for which ingestion was reported, a total 824 (88.4%) children swallowed the capsule uneventfully (95%CI: 86.4%-90.3%)[15]. The youngest child to swallow the capsule was 4 years old[23]. Only 1 patient in the reports could not swallow the capsule and refused endoscopic placement, although the inability to swallow the capsule or the fear of gagging and choking doing so are not infrequent occurrences in clinical practice[11].

A new diagnosis was established in 162 patients (66.0%; 95%CI: 45.4%-83.9%) including patients where the capsule did not enter the colon[12,17,18,23]. A change in therapy followed for 115 of the patients (71.3%; 95%CI: 45.2%-91.5%) where those parameters were quantified.

CD was the most prevalent diagnostic outcome of SBCE studies performed in the pediatric population, based on the criteria of at least 3 mucosal ulcers as previously reported by Fireman and colleagues[36] and Mow and colleagues[37]. In one study, SBCE examination reclassified 4 of 5 patients with UC and 1 of 2 patients with IC (total 5 of 7, or 71%) to CD due to newly recognized SB mucosal lesions[12]. In various studies, a change in medical therapy resulted for 75%-92% of patients with known CD[12,13,17].

A recent pilot study evaluating dietary intervention in pediatric CD[27] assessed small bowel mucosal change using CE since 38% of pediatric CD is isolated to the small intestine and 80% of pediatric CD have small bowel involvement[38]. Using the Lewis score, a validated, weighted index of 3 parameters (stenosis, ulceration and villous edema)[39], mucosal improvement was seen at 12 and 52 wk from baseline, providing objective evidence of mucosal change, which can be used to complement standard clinical IBD research scoring methods that can be affected by the subjective reports from the patients and their families. In pediatric patients investigated for OGIB or IDA by SBCE, 38.4% had confirmed diagnoses[14]. This compares with 59.4% positive results in adults[40]. Forty-six lesions were diagnosed by SBCE[8-11,13,18]: 15 vascular malformations, 7 CD; 14 nonspecific enteropathies; 3 polyps; 2 marked lymphoid hyperplasias; and 1 case each of Meckel's diverticulum, nonsteroidal anti-inflammatory drug-induced lesions, lymphangiectasia, leukemia-related- and graft-versus-host disease. In patients younger than age 8 years, there were 4 cases of polyps, 2 of angiodysplasias, 2 blue rubber bleb hemangiomas, 2 Meckel's diverticulae, 1 anastomotic ulcer, and 1 intestinal duplication[23]. In the adult meta-analysis, vascular abnormalities also were the most common cause of OGIB (50%), followed by inflammation and ulcers (27%), and neoplasia (9%)[40]. Evaluation of polyposis syndromes, accounted for 8.0% of the indications in 81 pediatric patients, with positive results in 80.2% of procedures compared to adult diagnostic yield of 55.9% for neoplastic lesions[41].

Although SBCE is rarely performed for evaluation of malabsorption, it is useful since intestinal lymphangiectasia can appear beyond the reach of the endoscope[5]. The infrequency of celiac disease seen in pediatric patients may reflect the infrequency of CE use for evaluation of malabsorption in this population[4] or the decreased time of gluten exposure with potentially patchy or very subtle mucosal changes in childhood at histological levels of Marsh I or II, for which the sensitivity of CE is low[42]. Although lymphonodular hyperplasia and intussusceptions are often seen, they are normally non-pathogenic conditions indigenous to the pediatric population[5].

Adverse events

Capsule retention in the SB occurred in 18 and gastric retention occurred in 4 of 1013 procedures in the meta analysis, producing a pooled retention rate of 2.3% (n = 22/1013; 95%CI: 1.5%-3.4%)[5-7,15]. Endoscopy was used to remove 5 capsules including 4 from the stomach[9-15] and 1 from an ileal pouch[5]; 13 were retrieved surgically while taking appropriate measures to mitigate the cause of the retention[8,10,13,17]. A retained capsule was successfully evacuated by bowel prep at 22 d post-ingestion[10].

The greatest risk factors for capsule retention include known IBD (5.2% risk), previous small bowel follow-through (SBFT) demonstrating small bowel CD (35.7% risk) and a body mass index below the fifth percentile combined with known IBD (43% risk), although retention has occurred despite the absence of stricture on SBFT[14]. Among 4 patients with CD having capsule passage lasting longer than 5 d (with 3 continuing on to retention), age was significant (18.8 ± 0.9 *vs* 14.6 ± 3.5), but not height or weight, compared to patients who did not have retention[17]. Retention rates for indications of OGIB, CD, and neoplastic lesions were 1.2% (95%CI: 0.9%-1.6%), 2.6% (95%CI: 1.6%-3.9%), and 2.1% (95%CI: 0.7%-4.3%), respectively, with a pooled rate of 1.4% (95%CI: 1.2%-1.6%) for those procedures[43]. On a per-procedure basis, this pattern is similar in adults, where retention in OGIB, CD, and polyps occurs at rate of 1.4%, 2.2%, and 1.2%, respectively[40]. Thus, it appears that the risk of retention is dependent on the clinical indication, with an higher incidence in patients with suspected chronic small bowel obstruction[43]. Rare cases of perforation, aspiration, or small bowel obstruction have been reported in adults but none have been reported in children. Minor mucosal trauma has occurred in children in which capsules were placed with the Roth net[21]. A specific capsule placement device is now available (AdvanCE, United States Endsocopy, Mentor, OH[44]).

Patency capsule: The majority of capsule retentions have occurred in patients with normal small bowel radiological studies, yet functional patency may be present in patients with radiologically documented strictures. To avoid this concern, an identically sized patency capsule (PC) containing a mixture of barium, lactose and a radiofrequency identity tag was developed. The first version had a single timer plug that degraded at 40 h. The currently available version has dual timer plugs that gradually implodes if passage does not occur within 30 h.

Both a retrospective[5] and a prospective study[45] have been performed in pediatric IBD using the first iteration of the PC prior to SBCE. Of the 19 who were evaluable in the retrospective analysis, patency was established and subsequent CE was performed successfully in all but 1 patient who had a retained capsule from CE the following week. The prospective trial of 18 patients (age 10-16 years) who ingested the PC, 15 of whom excreted an intact PC (mean 34.5 h) without any PC or CE retentions or adverse events[45]. CD was eventually diagnosed in all patients having PC transit of more than 40 h and in 9 of 12 who passed the patency capsule in 40 h or less. There were no capsule retentions or adverse events. Thus, the PC can serve as a useful guide and may lessen the likelihood of CE retention, particularly in known CD where the risk of retention is greatest.

Esophageal and colon capsules: Esophageal capsule endoscopy (ECE) was approved by the US FDA and introduced for clinical use in 2004 with a second iteration (ESO 2; Given Imaging) released in 2007. However, clinical trials and apparent pediatric use (or at least, the reporting of that use) have been limited. Only 2 small pediatric trials of the first ECE capsule have appeared. Both focused on portal hypertension, finding that variously sized varices and other esophageal and duodenal findings could be seen despite a rapid transit time in pediatric patients[46-48].

Similarly, colon capsule endoscopy (CCE; Given Imaging Ltd, Yoqneam, Israel)[49-54] has been aided by a recently released, second-generation CCE device (CCE-2)[51,52], Consensus guidelines of ESGE on CCE have proposed that CCE-2 may be useful to monitor inflammation in UC, which may help guide therapy[53]. To date, there have been few studies conducted in adults, with only one using the second generation of CCE[54-57]. There is only one pilot study using CCE-2 in 29 pediatric patients with ulcerative colitis[58]. Sensitivity of CCE-2 in detecting disease activity was 96% (95%CI: 79%-99%) and specificity was 100% (95%CI: 61%-100%), corresponding to an overall accuracy of 97% (95%CI: 90%-100%). The positive and negative predictive values were 100% (95%CI: 85%-100%) and 85% (95%CI: 49%-97%), respectively. Optimal preparation is yet to be adequately studied or established.

CONCLUSION

SBCE is a useful diagnostic tool that has particular benefit in pediatrics because it does not usually require ionizing radiation, deep sedation or general anesthesia. The risk of retention appears to be dependent on indication rather than age and parallels the adult experience by indication, making SBCE a relatively safe procedure with a significant diagnostic yield. Recent investigations to improve bowel cleaning and establish CE as a useful tool to monitor mucosal change may further expand its utility.

The limited data on ECE and CCE in pediatrics do not warrant the same conclusions as yet; however, both appear to provide safe methods to assess and monitor mucosal change in their respective anatomic areas with little discomfort. However, further investigations are needed to maximize the impact of this burgeoning area of mucosal assessment and to determine whether CE can pre-empt traditional studies in order to lessen cost and improve tolerability of needed procedures.

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