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ORIGINAL ARTICLE

Role of wireless capsule endoscopy in reclassifying inflammatory bowel disease in children☆

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Abstract

Objective: To evaluate the role of wireless capsule endoscopy in identifying small bowel lesions in pediatric patients with newly diagnosed colonic inflammatory bowel disease (IBD) type unclassified (IBDU), and to assess whether capsule endoscopy findings result in altered patient management.

Methods: Ten pediatric patients recently diagnosed with IBDU through standard investigations were recruited from the pediatric gastroenterology clinic at McMaster Children's Hospital to undergo capsule endoscopy using the Pillcam SB™ (Given Imaging) capsule. Findings consistent with a diagnosis of Crohn's disease required the identification of at least three ulcerations.

Results: Three out of ten patients had newly identified findings on capsule endoscopy that met criteria for Crohn's disease. Three more patients had findings suspicious for Crohn's disease, but failed to meet the diagnostic criteria. Three additional patients had findings most consistent with ulcerative colitis, and one had possible gastritis with a normal intestine. Findings from capsule endoscopy allowed for changes in the medical management of three patients. In all ten cases, capsule endoscopy allowed for a better characterization of the type and extent of disease. No adverse outcomes occurred in the present cohort.

Conclusion: This prospective study reveals that wireless capsule endoscopy is feasible, valuable, and non-invasive, offering the ability to potentially better characterize newly diagnosed pediatric IBDU cases by identifying lesions in the small bowel and reclassifying these as Crohn's disease.

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PALAVRAS-CHAVE
Cápsula endoscópica;
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Pediátrico

Papel da cápsula endoscópica na reclassificação da doença inflamatória intestinal em crianças

Resumo

Objetivo: Avaliar o papel da cápsula endoscópica na identificação de lesões no intestino delgado em pacientes pediátricos com DII inespecífica (DIII) diagnosticada recentemente e avaliar se os achados da cápsula endoscópica resultam em alterações no tratamento dos pacientes.

Métodos: Dez pacientes pediátricos recém-diagnosticados com DIII por meio de investigações padrão foram recrutados da clínica de gastroenterologia pediátrica no McMaster Children's Hospital, para serem submetidos a exame com a cápsula endoscópica Pillcam SB™ (Given Imaging). Achados compatíveis com o diagnóstico da doença de Crohn exigiram a identificação de pelo menos três ulcerações.

Resultados: De 10 pacientes, três apresentaram achados novos com a cápsula endoscópica que satisfizeram o critério para a doença de Crohn. Outros três apresentaram achados com suspeita de doença de Crohn, porém não atenderam nossos critérios de diagnóstico. Apresentaram achados mais compatíveis com colite ulcerativa outros três pacientes, e um apresentava possível gastrite com intestino normal. Os achados da cápsula endoscópica possibilitaram mudanças no tratamento médico de três pacientes. Em todos os dez casos, a cápsula endoscópica permitiu uma melhor caracterização do tipo e da extensão da doença. Não houve resultado adverso em nossa coorte.

Conclusão: Este estudo prospectivo revela que a cápsula endoscópica é viável, útil e não invasiva, que oferece a possibilidade de melhor caracterização de casos de DIII pediátricos recém-diagnosticados ao identificar lesões no intestino delgado e reclassificá-las como doença de Crohn.

Introduction

Inflammatory bowel disease (IBD) is increasing in prevalence among children. Using current standard investigations, between 5% and 20% of newly identified cases of IBD with pure colonic involvement cannot be definitively categorized as Crohn's disease (CD) or as ulcerative colitis (UC).[1,2] This translates to an incidence of 1.6-2.4/100,000 of "indeterminate" IBD, otherwise known as colonic IBD type unclassified (IBDU).[1] A diagnosis of indeterminate colitis is based on clinical and endoscopic features, along with indeterminate histologic samples revealing areas of minimal to moderate glandular distortion alternating with areas of regular epithelium, and presence of inflammatory cells in the basal part of the lamina propria.[1,3,4] Some authors suggest that the term "indeterminate colitis" should be reserved for patients with surgical specimens, while the IBDU should be used for patients without surgical specimen.[1] Regardless of the term used, without a clear diagnosis, management of these patients is obscure, based on clinical suspicion, and modified by trial and error. Establishing the specific disease process early on is likely to present clinical benefits by allowing for earlier institution of appropriate management.

Wireless capsule endoscopy (WCE) is a novel tool that provides detailed color images of the gastrointestinal tract. The wireless capsule offers non-invasive visualization of large spans of the small intestine that are otherwise not entirely accessible by upper and lower endoscopy. The capsule, measuring 11 mm x 26 mm, transmits images at a rate of two frames per second, and has a battery life of six to eight hours.[5] In adults, capsule endoscopy has been found to be clinically useful in managing confirmed or suspected cases of IBD. The diagnostic yield of WCE in confirming suspected CD in adults ranges between 38% and 75%, depending on the study and the criteria used to suggest underlying CD.[6] While WCE is potentially useful to categorize IBDU patients, a negative WCE does not exclude a future diagnosis of CD.[1]

At present, capsule endoscopy has been used in a limited fashion in pediatric patients. The goal of this pilot study is to investigate the role of WCE in identifying small bowel lesions not otherwise identified by current standard investigations in pediatric patients with newly diagnosed IBDU.

Methods

This was a prospective study to recruit patients from the McMaster Children's Hospital pediatric gastrointestinal clinic who were diagnosed with IBDU via standard

evaluation between the years of 2008 and 2009. Routine investigations included: complete blood count, erythrocyte sedimentation rate, C-reactive protein, albumin, ferritin, anti-*Saccharomyces cerevisae* antibodies, p-anti-neutrophil cytoplasmic antibody, small bowel follow through (SBFT), as well as upper and lower endoscopies. Inclusion criteria were patients with IBDU, between 5 and 17 years of age, who had a normal SBFT prior to capsule endoscopy. Exclusion criteria were previously established diagnoses of CD or UC, with an abnormal SBFT. Being a novel pilot study, the current standard of investigation and of care was used for comparison. The Ethics Review Board of the McMaster Children's Hospital approved the study; an informed consent was obtained from all patients.

In the pediatric gastrointestinal laboratory, nine patients swallowed a Pillcam SB™ (Given Imaging) capsule following a 12-hour fast. A single patient was unable to swallow the capsule secondary to anxiety, so endoscopic insertion with a Roth Net was employed in this case. In all cases, no bowel preparation was used. Once the capsule was ingested, patients were instructed not to drink for the first two hours, and not to eat for the first four hours after the beginning of the study. WCE images were later downloaded to the workstation. Two weeks after completion of the study, an abdominal radiograph was performed if the capsule had not been observed to have been eliminated in the stool. All patients were followed regularly in the routine IBD clinic. The duration of study involved a six-month period of enrolment, and a follow-up of 12 months for each patient. Study images were reviewed by an experienced gastroenterologist (AS). Adequacy of capsule endoscopy required good quality images capturing the terminal ileum or cecum. Since criteria for the diagnosis of CD via WCE has not been established or validated to date, stringent criteria adopted from the adult literature were implemented. Three or more ulcerations in the small intestine visualized by WCE were required in order to be consistent with a diagnosis of CD.[7] Ulcers were characterized by lesions within a crater with surrounding erythema, whereas erosions were described as superficial white lesions with surrounding erythema.[7] Isolated erosions, villous atrophy, and mucosal breaks were not considered evidence of CD.

The primary outcome was to determine whether capsule endoscopy would identify new small bowel lesions in patients with IBDU that were not recognised via conventional studies, and to assess whether these newly identified lesions fulfil the criteria adopted to suggest CD. As a secondary outcome, it was evaluated whether findings from WCE allowed for changes in medical management. Descriptive statistics including range, frequencies, proportions, and medians were used to describe the study population. All adverse events were recorded.

Results

Ten patients with the diagnosis of IBDU who met the inclusion criteria were consecutively recruited. Their demographic and clinical characteristics are listed in Table 1, as well as the findings from the standard investigations. In all ten cases, images were of great quality and image adequacy was met. In fact, for all cases, images provided a better characterization of the location and extent of disease. There were no cases of retained or impacted capsules, and no abdominal radiographs were required. No adverse events occurred in the present cohort.

WCE allowed for the identification of lesions meeting the adopted criteria suggestive of CD in three of ten patients. Three additional patients had findings suspicious for CD, but failed to meet the outlined criteria. Three others had large intestine pathology most consistent with UC. The last patient had a normal appearing intestine; however, WCE images were suggestive of esophagitis, and he was later confirmed to have a fungal esophagitis, when upper endoscopy was repeated.

Modifications in patient management attributable to data gained by WCE included both intensification and de-escalation of treatment. Overall, three patients had a change in medical management in light of findings obtained by WCE.

Discussion

WCE is a valuable tool that offers a non-invasive means of obtaining high quality images of the mucosal lining of the gastrointestinal tract, including segments that are not accessible with conventional methods. WCE is particularly convenient and advantageous in the pediatric population, as it does not require bowel preparation, radiation, general anaesthesia, or IV deep sedation.[8] Sant'Anna et al. were the first to explore the use of WCE in identifying obscure disorders of the small intestine in pediatric patients.[9,10] Since then, the application of WCE in pediatric gastroenterology has grown to include numerous roles, including the investigation of IBD.[8,11-15] The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition has concluded that WCE has a role in the identification of CD in the small intestine.[11] Though capsule impaction is a major risk of WCE, occurring in approximately 3.5% of pediatric patients,[16] the United States Food and Drug Administration (FDA) has approved the use of WCE in children over the age of 2 years.[17,18] Others report that WCE is feasible and safe in children as young as 1.5 years old.[12]

The major predicament of WCE is the inability to concurrently sample tissue for histologic confirmation of disease.[5,14,19-21] Although integration of tissue sampling in WCE is underway,[22] gastroenterologists are currently left without a gold standard to assess the accuracy, sensitivity, or specificity of WCE findings.[23] Non-steroidal anti-inflammatory drugs (NSAID) usage has been associated with a high prevalence of bowel injury, necessitating the discernment of these lesions from those of underlying IBD.[24] More troublesome is that mucosal breaks have been identified in the small intestine of 15% of normal subjects, in absence of NSAID use.[1,25] Without histological confirmation of the etiology of suspicious lesions visualized through WCE, it is impossible to determine with certainty which are evidence of CD.[24] Moy et al. found that WCE findings of ulcerations or strictures are highly suggestive of CD and respond to therapy, while erosions alone are not sufficient to diagnose CD, and should not be used to guide medical therapy.

Table 1 Demographic and clinical characteristics and findings from the standard investigations for the study patients.

Patients (n = 10)	Results
Age (years); median (range)	14.7 (9.8-17.8)
Gender; male: female	7:3
Weight (kg); median (range)	48.9 (27.5-68.1)
Height (m); median (range)	1.61 (1.34-1.73)
Body mass index (kg/m²); median (range)	19.3 (14-22.6)
EGD; n (%)	
Normal	7 (70%)
Mild gastritis	1 (10%)
Duodenal nodularity	1 (10%)
Mild esophagitis	1 (10%)
Colonoscopy; n (%)	
Microscopic colitis (normal macroscopy)	2 (20%)
Superficial continuous ulceration of the right colon	3 (30%)
Superficial continuous ulceration of transverse and left colon	3 (30%)
Multiple tiny aphthous ulcers of the recto sigmoid	2 (20%)
SBFT; n (%)	
Negative	10 (100%)
p-ANCA; n (%)	
Negative	10 (100%)
ASCA; n (%)	
Negative	10 (100%)

ASCA, antisaccharomyces cerevisae antibodies; EGD, esophagoduedenoscopy; p-ANCA, p-anti-neutrophil cytoplasmic antibody; SBFT, small bowel follow through.

The present study faces the collective limitation of having no gold standard upon which to compare WCE findings, precluding definitive determination of CD. Given such currently inescapable limitations, the most stringent criteria adopted from adult studies were implemented, while abiding by Moy et al.'s findings so as to limit false positive cases of CD identified by WCE. WCE was unique in identifying convincing evidence to reclassify three of ten patients as having lesions consistent with CD, where standard investigations failed to identify such lesions. WCE also provided objective findings instigating the appropriate modifications in the medical management of three patients. Additionally, there were no cases of capsule retention in the present cohort, and good quality WCE images were obtained in every case. Though a limiting factor, a small sample size is acceptable for the purpose of the present feasibility study. One point worth mentioning is that the study sample a highly select population of IBDU, which limits the assessment of the WCE utility. The best way to assess the diagnostic utility of the WCE would be by including an unselected population of IBD undergoing the diagnostic tests, and comparing WCE with the standard investigations to formally assign the IBD diagnosis. However, due to the cost of this test, it is more appropriate to reserve it for those with IBDU diagnosis.

Several retrospective studies addressed the use of WCE in identifying small intestine lesions among pediatric patients. Oloughlin et al. retrospectively studied the utility of WCE in detecting small intestinal lesions suggestive of CD in 24 children, where eight cases met criteria for CD.[26] Moy and Levine performed a larger retrospective review of 46 WCE in children for various indications, including unresponsive CD and UC.[27] In their study, WCE revealed nine new cases of CD.[27] They also compared the diagnostic yield of WCE and small bowel series (SBS) in children being evaluated for small bowel disease, and concluded that WCE revealed 100% of the pathology identified by SBS, whereas SBS only recognized 47% of those identified by WCE.[27] This group later studied the use of WCE in children with unexplained growth failure, in whom Celiac disease and Crohn's disease were excluded via standard tests.[28] Four of the seven patients investigated had small intestine lesions consistent with CD, and upon initiation of therapy, all gained weight and experienced symptomatic improvement.[28] Similarly, De'Angelis et al. retrospectively investigated the diagnostic value of WCE in ten Italian children with suspected CD that could not be confirmed by endoscopy, where WCE showed active lesions suggesting CD in five cases.[17] Cohen et al. retrospectively evaluated the use of WCE in 28 children with established CD, UC, or IBDU experiencing exacerbation or growth failure.[29] Here, WCE identified small bowel lesions resulting in the reclassification of four of the five patients previously diagnosed with UC, and one of the two patients with IBDU was reclassified as having CD.[29] These studies highlight the potential diagnostic value of WCE, along with its prospect in allowing changes in medical management and offering clinical improvements by identifying lesions consistent with CD not otherwise documentable.[28]

Although suggesting a role in identifying WCE as a novel tool in better categorizing patients with IBDU, the retrospective nature of the above studies limits their validity. To date, very few prospective studies have been performed in pediatric patients using WCE in the investigation of IBDU. Thomson et al. assessed the diagnostic yield of WCE in 28 children

with various types of small bowel disease.[8] In their cohort, 16patients were known to have CD, and WCE revealed a greater extent of small bowel lesions consistent with CD than did a barium meal follow through.[8] However, this group did not assess the evaluation of IBDU with WCE. Fritscher-Ravens et al. performed a large prospective European multicenter study a looking at numerous gastrointestinal diseases among 83 children between 5 and 8 years of age.[12] Within this study, 20 had suspected CD that could not be confirmed using standard investigations.[12] In this study, WCE identified diffuse aphthous ulceration, fissuring, and terminal ileitis in 11 of these 20 patients.[12] Arguelles-Arias et al. prospectively studied the use of WCE in 12 pediatric patients over 12 years old with a suspicion of CD that could not be otherwise confirmed.[23] They applied a broad range of diagnostic manifestations, including aphthae, mucosal fissures, erosions, and linear or irregular ulcers, and concluded that WCE identified CD in seven of 12 patients.[23] The present study differs from this one in two respects, which likely explains the divergent proportion of patients identified as having CD by WCE (seven of 12 patients in their study *versus* three of ten in the present study).[23] In the present study more stringent criteria were applied to establish a high suspicion of CD, and a more comprehensive age group was analyzed, including a higher proportion of younger patients, who are less likely to have underlying IBD, . More recently, Gralnek et al. identified lesions suggestive of CD in two out of three patients with indeterminate colitis, using criteria similar to that of the present study, providing corroborative evidence that WCE is useful in identifying lesions not otherwise identified endoscopically.[30]

Unlike studies performed to date including adult studies, retrospective pediatric studies, or pediatric studies addressing a variety of gastrointestinal diseases at once, the present study prospectively and specifically addressed pediatric patients with IBDU who could not be better classified using standard investigations. By explicitly addressing this issue, it can be concluded that there is strong potential for the clinical utility of WCE in better characterizing IBDU. Though not tested in this study, it is anticipated that such earlier identification will translate into improved patient management and outcome. These findings emphasize the need for continued investigation, with large prospective randomized control trials with longer follow up periods to further assess the role of WCE in reclassifying puzzling cases of IBDU, as well as to assess changes in medical management and anticipated improvements in disease progression.

Conflicts of interest

The authors have no conflicts of interest to declare.

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