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Review

Applications of wireless capsule endoscopy in pediatric age: an update

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Summary. *Background:* The small bowel has often been considered the mysterious "black hole" of the gastrointestinal tract. With regards to this, the development of the wireless capsule endoscopy (WCE) has represented a turning point. It is a non-invasive technique, enabling an excellent visualization of the small bowel (SB) mucosa without the use of radiation. The WCE was approved by the Food and Drug Administration (FDA) in 2001 for adults and in 2004 for children. The aim of the present review is to provide an update on indications, diagnostic yield, safety and limitations of WCE in children. Even though literature regarding the use of WCE in pediatric age is more limited than in adults, WCE is a useful and safe diagnostic tool for the exploration of the small bowel also in children. The indications for WCE are similar at any age, however the main indication in children is Crohn's disease (CD), while in the adults is the research of SB bleeding. The main limitation in pediatric age is the possibility for younger children to swallow the capsule. WCE in pediatric is a rapidly advancing technology and has the potential to further transform the evaluation and management of SB disease. (www.actabiomedica.it)

Key words: wireless capsule endoscopy, pediatrics, small bowel diseases, indications, safety

Introduction

The small bowel has often been considered the mysterious "black hole" of the gastrointestinal tract. With regards to this, the development of the wireless capsule endoscopy (WCE) has represented a turning point. It is a non-invasive technique, enabling an excellent visualization of the small bowel (SB) mucosa without the use of radiation. The WCE was first used in humans in 1999, in 2001 it was approved by the Food and Drug Administration (FDA) as an adjunct tool for the evaluation of SB diseases in adults and later 2003 as a first-choice diagnostic method for investigating SB diseases. In 2004 WCE was approved as a diagnostic tool also for children of 10 years or older.

Supported by additional experience in younger children, in 2009 the FDA expanded the diagnostic role of WCE and of the patency capsule (PC) for their use in children of two years or older (1). Patency capsule is a capsule with identical size of a standard capsule, containing a mixture of barium, that gradually dissolves if passage does not occur within 30 hours from the administration.

Anyway, case reports have demonstrated a safe use also in younger children, down to 8 months or 7,9 kg (2, 3). Overall, the use of WCE in children has some limitations mainly due to eventual difficulties for children in swallowing the capsule, and due to a scarcity of literature in pediatrics. The present review will provide data on the indications, diagnostic yield, safety and limitations of WCE in children.

Wireless capsule endoscopy

Nowadays, four types of small bowel capsules (PillCamSB, EndoCapsule, Miro capsule, and Capso Cam) and one esophageal capsule (PillCam ESO) are available. A capsule for the exploration of the colon is also available in Europe, in the United States and in Japan (Pill Cam Colon). The PillCam is now a third-generation capsule, with improved resolution and a variable frame rate. The frame rate increases to six frames per second when moving quickly and slows to two frames per second when moving slowly or when it is stationary. The EndoCapsule is similar to Pillcam but has a charge-coupled device chip instead of a complementary metal oxide semiconductor chip. The EndoCapsule has been replaced by the endoCapsule10 with increased resolution and three-dimensional location software.

The Miro Cam capsule uses a novel mode of transmission called electric field propagation, which uses the human body as a conductive medium to transmit images (4).

The CapsoCam is equipped with four cameras giving a 360° field of view and a variable frame rate. Wireless capsule evolution sees not only a continuous improvement in the optical lenses and image resolution, but also the software present constant advances. The resolution of modern capsule images is at a maximum 512x512 pixel (5). With the help of software algorithms picture, quality is enhanced to provide enough details for all relevant findings.

Unfortunately, there are no commercially available capsules capable of taking biopsies yet.

At present, all the capsule devices available have a battery life of 12 hours or grater. This extended battery life reduces the chance of incomplete transit in the non-obstructed small bowel.

Indications and diagnostic yield

Certainly, WCE has represented a great advance in the study of SB disease in adults. Similarly, in pediatric age, as it is a non-invasive technique which avoids the use general anesthesia and ionizing radiation, WCE represents a real advantage in diagnostic, therefore its use has experienced a significant expansion. The are several important differences in the use of WCE between adults and children (6). In pediatrics, one of the most important considerations to be made before undertaking WCE is the evaluation of the patient's ability to swallow the capsule. Patients may be helped learning to swallow the capsule, by practicing swallowing candies (7). According to reported evidence, the most physiologic way to proceed is swallowing the capsule with some water, which is safe feasible even for children 4 to 5 years old (8). In a review by Cohen et al, including 824 children among whom the youngest was 4 years old, 88,4% of the patients were able to swallow the capsule (6). Anyway, the ability to swallow the capsule is not exclusively dependent on age. Up to 1,1-1,5% of adults and older children are unable to ingest the capsule that is bigger than 1x2 cm in size. In case of impossibility for the patient to swallow the capsule due to any reasons (including swallowing disorders, dysphagia, etc.), the capsule can be safely delivered into the duodenum with various techniques during a standard endoscopy (9, 10). There are different devices for endoscopic capsule delivery, such as polypectomy snares, foreign body baskets or specific delivery devices (11) (Figure 1).

The advanCE device allows endoscopic delivery of the capsule. The system is a disposable catheter with a sheath diameter of 2,5 mm that can be preloaded through the appropriate operative channel of a standard endoscope. The placement of the capsule into the duodenum is relevant to ensure the visualization of the entire SB, avoiding the risk of delay in the passage from the stomach to the duodenum which is frequent when the capsule is swallowed. Sometimes, especially in younger children, only the tip of the endoscope may

Figure 1.

be driven into the duodenum, consequently the capsule may return into the stomach. Moreover, is case of endoscopic capsule delivery, the patient should be sedated and eventually intubated (12).

In 2015 a panel of experts in the field of WCE belonging to the Spanish Society for Pediatric Gastroenterology, Hepatology and Nutrition (SEGHNP) and to the Spanish Society for Digestive Disease (SEPD) established guidelines for the use of WCE in children (12).

The indications for the use of WCE are similar in children and adults, (table 1) however according to the available scientific evidence, the most frequent indication for WCE in children is inflammatory bowel disease (IBD) both for diagnosis and disease extension assessment, while it is the diagnostic of obscure gastrointestinal bleeding (OGIB) in adults (6). On the other hand, obscure gastrointestinal bleeding, malabsorption and protein-losing enteropathies, small bowel polyps, tumors and in general all the clinical situations where small bowel pathology is suspected are other reported indications for WCE in pediatric population, as in adults (13, 14).

A recent study regarding the use of WCE in children compared indications for WCE among 1013 procedures in pediatric patients and 22840 procedures in adults and concluded that in pediatric patients, 63% of WCE had been performed for Crohn Disease (CD), 15% for OGIB, 10% for abdominal pain/diarrhea and 8% for polyposis (15). In contrast, in adults 66% of WCE had been performed for OGIB and 10% for CD (16). However, it is of note that OGIB is more frequent than CD in pediatric population younger than 8 years of age (6).

Table 1. Indications to perform small bowel Wireless Capsule Endoscopy

Indications for small bowel WCE in children
Small bowel Crohn's disease
Diagnosis and extent evaluation
Occult/obscure intestinal bleeding
Small bowel polyps
Familial and non-familial polyposis
Malabsorption and protein losing enteropathies
Celiac disease
Eosinophilic and food allergic enteropathies
Intestinal lymphangiectasia
Small bowel tumor
Lymphoma
Leiomyoma
Carcinoid and other

Wireless capsule endoscopy and Inflammatory Bowel Disease (IBD)

In the investigation of IBD, WCE may be used at different times during the course of the disease: at diagnosis, in the differentiation of ulcerative colitis (UC) or indeterminate colitis (IBDU) from CD, in the investigation of CD extension, activity, response to treatment, or later in the disease course to differentiate active disease from contemporary functional complaints (17).

In 2009 the world Organization of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organization (ECCO) recommended to perform WCE in children for the diagnosis of CD when conventional upper and lower endoscopy and radiographic imaging are not conclusive (18). The recommendations of ESPGHAN have established that WCE is a useful alternative to identify small bowel mucosal lesions in children with suspected Crohn disease in whom conventional endoscopy and imaging tools have been non-diagnostic or in whom Magnetic Resonance Enterography (MRE) cannot be performed due to young age or in settings where MRI is not available or not feasible. A normal WCE study has a high negative predictive value for active small bowel CD (19). The main advantages of WCE are the ability to visualize the entire small bowel with minimal disconfort and to detect mucosal lesions with a higher sensitivity than MRE. The risk of capsule retention, and the inability to control capsule movement are the main limitation (20). It is therefore recommended that MRE or Patency capsule should precede WCE in order to identify strictures that may cause capsule retention (12). Moreover, WCE has a high rate of incidental findings, and therefore a low specificity. False positive features are found in 10-21% of healthy people, particularly in case

of non-steroidal anti-inflammatory drugs use which can cause erosions and ulcers. In a meta-analysis in pediatric onset IBD the diagnostic yield for WCE ranged from 58 to 72% whereas it was 0 to 61% for ileocolonoscopy (16). In a prospective pediatric controlled study conducted on 20 children with suspected IBD with either normal or non-specific findings on conventional imaging, WCE confirmed the diagnosis of CD in 12 (60%) (21). In different reports both sensitivity and specificity of WCE range from 77,8% to 94,6% while MRE shows a sensitivity of 75-85,7% and a specificity of 70% (22). Anyway, both MRE and CE should be considered complementary and accurate methods in patient with suspected CD (23).

Intestinal polyposis

A few well-designed large studies have been reported that evaluate the use of WCE for the diagnosis and surveillance of small intestinal polyposis. Peutz-Jeghers syndrome (PJS) is the most frequent polyposis syndrome during childhood. PJS is associated with chronic bleeding, anemia and bowel obstruction and intussusception requiring surgery. Polyp related complications could develop in childhood since the age of 10 years. Guidelines recommend screening patients with PJS every 2 to 3 years beginning around the age 8 years for small bowel polyps, and earlier if symptomatic (24). Mostly retrospective case series have shown WCE to be an accurate diagnostic tool compared with small bowel through imaging of the intestine (13). Tomasa et al have raised concern about the use of WCE for polyp screening because of reports of proximal jejunal, duodenal polyps and tumors that were missed by WCE and properly identified by double balloon enteroscopy (DBE) (25). Ohmiya et al found no difference in the detection rates of either all type of polyps or large polyps (>10 mm) (26). Postgate et al compared the yield of WCE with the one of barium enterography in children with PJS and concluded that WCE is a feasible, safe and accurate tool for small bowel polyp surveillance in children with PJS (27). Moreover, the assessment of polyposis syndrome has the highest diagnostic yield by indication of WCE in children. Around 80,2% of the procedures lead to significant findings, a greater percentage than in adults. Hence, WCE should be considered as a first line diagnostic method in small bowel polyposis syndrome. Studies in children and adults with PJS and other small bowel polyposis syndromes will need to be performed to clarify the relative roles of DBE, CE and MRE in these clinical conditions.

Obscure gastrointestinal bleeding and iron-deficiency anemia

OGIB, whether occult or apparent, is the most frequent indication for CE in children younger than 8 years (16). Positive findings have been reported in 42% of pediatric patients (16) compared to 60% in adults with OGIB or persistent iron deficiency anemia (28). It is important to take into account that active bleeding lesions are more likely detected when WCE is used within the first 3 days (95%) or 2 weeks (93,1%) after the bleeding event, compared to more delayed procedures (57,1% after 2 weeks) (29). WCE may be useful in several gastrointestinal disorders in childhood, such as celiac disease, protein losing enteropathy, intestinal lymphangiectasia, graft versus host disease, chronic abdominal pain and failure to thrive. However, regarding these conditions, only data on isolated case reports have been published and scientific evidence is low.

Preparation

The inability to establish the exact location of the capsule in the small bowel and the inability to flush or aspirate make adequate bowel cleaning particularly important for SB WCE (30). Since cleaning the small bowel prior to examination may improve the diagnostic yield, CE preparation regimens have been proposed, mainly by using the same products adopted for colonoscopy preparation (31). The optimal preparation regimen is yet to be established. A meta-analysis study in adults demonstrated that a protocol including a combination of simethicone and polyethylene glycol appears to be the best approach. Oliva et al, in their randomized single blind study in children, demonstrated that low volume PEG (25 ml/kg) assumed the

evening before the study and 376 mg simethicone in 20 ml water 30 minutes before the procedure achieved better visualization scores (32). A 10-12 hour fasting before the testing is generally recommended.

Adverse events

WCE is, in general, a well-tolerated and safe procedure. Two complications have been noted in WCE, namely capsule retention and capsule inhalation. Capsule inhalation is an extremely rare event and has not been reported in children (33); this complication is observed particularly in individuals with neurological or swallowing disorders (34-35). The main complication of WCE in children is capsule retention in the small bowel, defined as missed expulsion of the capsule within 2 weeks from the administration or the need for directed intervention before that time. Its incidence in most studies ranges from 1,5 to 3,5%. However, there are numerous series in which this complication was not observed (36, 37) and series that reported retention in about 20% of procedures (38). Several risk factors have been associated with capsule retention. Firstly, it might be thought that patient size may play a role. However, this is not clearly observed in published pediatric series. Younger children may have more difficulties in swallowing the capsule, but they do not retain it more often than adults. Retention usually relates to an intestinal stricture, which may be inflammatory (e.g. CD, nonsteroidal anti-inflammatory drug enteropathy, and actinic enteritis), post anastomotic or due to the presence of small bowel intestinal tumors (28). Retention associated with the presence of polyps has also been reported in pediatrics (6, 33). Studies conducted both in adult and in pediatric age have demonstrated the usefulness of patency capsule in predicting the uneventful passage of the capsule (10). Retained capsules may resolve in time and therefore, if bowel obstruction does not occur, removal may be delayed. Capsules retained due to small bowel strictures, causing bowel obstruction, may need to be removed endoscopically or surgically; however, if an inflammatory stricture is suspected and the scenario does not show a clinical emergency, medical treatment of the underlying condition (e.g. steroids for inflammatory strictures) may be attempted before surgical intervention (39).

Patency capsule

Patency capsule (PC) is a capsule of identical size of a standard capsule and consists of a small identification tag (RFID), detectable by radiofrequency, which is surrounded by an absorbable material with a small amount of barium, all this covered by an external cover. 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 hours from the administration. Both retrospectives (40) and a prospective (41) studies have been performed in pediatric IBD using PC prior to WCE. In the retrospective analysis, a PC before WCE in 23 patients allowed 22 WCE to proceed with only 1 retained capsule. In the prospective trial conducted on 18 patients (age 10-16 years) who ingested the PC, 15 excreted an intact PC without any PC or WCE retentions or adverse events. The PC can serve as a useful tool before performing WCE, as it may lower the likelihood of WCE retention, particularly in known or suspected CD where the risk of retention is the greatest.

Conclusions

WCE is a useful and safe diagnostic tool for small bowel that has particular benefits in children, because it does not usually require ionizing radiation, deep sedation or general anesthesia.

The indications for performing WCE in children are similar to those in adults, however the main one in children is CD to establish both a diagnosis and disease extension, while it is obscure gastrointestinal bleeding (OGIB) in adults and in children younger than 8 years of age.

Moreover, only few limitations in the use of WCE are known in children. The main one is the difficulty for younger children to swallow the capsule, which turns WCE into an invasive method because of the

need to deliver the WCE into the duodenum using an endoscope under deep sedation or general anesthesia.

The risk of retention appears to be dependent on indication rather than the age of the patient, confirming that WCE is a safe procedure with a significant diagnostic yield.

WCE is a rapidly advancing technology and has the potential to further transform the evaluation and management of SB disease, even in pediatric age. Although it has evolved significantly since 2000, many areas for further research are open.

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