Video Capsule Endoscopy: The Past, Present, and Future
Bradford A. Whitmer*, Michael Raphael and Bradley Warren
St. John Providence Health System, USA

Abstract

Video capsule endoscopy (VCE) has been available for evaluation of the small bowel since the beginning of the 21st century. This review of the literature examines the beginnings of capsule endoscopy, improvements made, and capsules likely to be made available in the near future. Preparation, indications, contraindications, and future applications are also discussed.

Keywords: Video capsule endoscopy; Pillcam; Endocapsule; Mirocam; Gastrointestinal bleed; Iron deficiency Anemia; Crohn’s disease; Celiac disease; Small bowel tumor; Pillcam eso; Pillcam colon

Introduction

Video Capsule Endoscopy (VCE) started in its infancy as a way to image the small bowel, and is evolving as a method to visualize the entire gastrointestinal tract from mouth to anus. This review examines what VCE has accomplished so far, and what this relatively new diagnostic modality may have in store for gastroenterologists in the near future.

History

Capsule endoscopy was first approved by the FDA in August 2000 [1,2]. The first capsule was manufactured by Given Diagnostic Imaging Systems, called the M2A Plus capsule and then remarkeTmed as the PillCam SB. The PillCam SB measures 11mm x 26mm and weighed 3.7g. This capsule provides a 140 degree field of view, 1.8 magnifications, one to thirty mm depth of view, and a minimum size of detection of about 0.1 mm. The battery lasts six to eight hours and transmission occurs at two frames per second. Color images are composed of 256 x256 pixels [3].

In 2007, the second generation PillCam SB2 improved optics by increasing from one lens to three lenses, developed an advanced automatic light control, and increased the field of view from 140 degrees to 156 degrees. While similar in diagnostic yield, a study revealed improvements in homogenous light exposure, sharpness, resolution, depth of view and overall impression when comparing the PillCam SB2 to the original PillCam [4].

The Endocapsule by Olympus Medical Systems was approved by the FDA in October 2007. While similar in size and shape, it has a couple of notable differences. It uses a charge coupled device (CCD) instead of complementary metal oxide silicon (CMOS) as its image sensor and uses a higher number of pixels per image 512 x 512. Angle of view is 145 degrees. Studies have shown comparable diagnostic findings when comparing the Endocapsule to the original PillCam SB [5,6].

The Mirocam by IntroMedic is not yet FDA approved and is currently in studies. This capsule uses different technology to transmit data to its receiver called electric field propagation. It uses the human body as a conductive medium, rather than radio waves. The capsule is 11 x 24mm, has a battery life of greater than 11 hours, and a frame rate of 3 per second. It has an angle of view of 150 degrees and uses a 320 x 320 pixel resolution.

The OMOM capsule by Jinshan Science and Technology is the largest at 13 x 28mm. It is also not FDA approved. It has the highest pixel number at 640 x 480, a battery life of eight hours and a 140 degree angle of view. It is unique due to bi-directional signaling. Both the lighting and the rate of image capture, up to 15 per second, can be adjusted with this capability, which is the first commercial demonstration of two-way transmission. In China, this capsule has been found to have similar diagnostic rates as the PillCam SB, but at half the cost [7].

Specific capsules have been introduced to evaluate more than just the small intestine. Pillcam ESO was approved in October 2004 to evaluate the esophagus. This capsule captures seven frames per second from each end for a total of fourteen frames per second. The capsule battery life is only twenty minutes [8].

A second generation capsule has been released called the Pillcam ESO2. Each CMOS captures nine frames per second, bringing the total frames to eighteen per second. The ESO2 also has advanced optics with three lenses instead of one. It uses automated lighting instead of fixed, and angle of view is increased to 169 degrees. Compared with EGD for detecting suspected Barrett’s esophagus and esophagitis, the PillCam ESO2 had a sensitivity of 100% and a specificity of 74%, and a sensitivity of 80% and a specificity of 87%, respectively. The PillCam ESO2 demonstrated 86% agreement with EGD in describing the Z line [9].

Preparation & Administration

No clear consensus on preparation is yet available. It is generally accepted that patients should fast for at least 12 hours before. The use of polyethylene glycol has been debated. A purgative may help eliminate food residue, air bubbles and bile. A meta-analysis of 12 studies comparing video capsule endoscopy with and without a purgative (PEG or sodium phosphate) revealed better visualization and higher diagnostic yield [10]. The amount of polyethylene glycol to be used has also been studied. Two liters of PEG has been found to be superior to none at all, but four liters of PEG has not been found to be of any further benefit [11,12].

On the day of capsule ingestion, sensors are attached to the patient to receive information from the capsule. For the PillCam SB2, a belt is worn which contains the sensors. For the Endocapsule, a sensor array is attached to the abdomen by adhesive pads. The sensors are connected to a data recorder which is powered by a battery pack.

*Corresponding author: Bradford A. Whitmer D.O., St. John Providence Health System, USA, E-mail: whitmer5@msu.edu

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The capsule is then swallowed with water. A diary of symptoms should be kept and the patient should monitor the lights on the data recorder to confirm that the signal is being received. A diet of clear liquids is allowed after two hours and food or medications after four hours. The data recording system can be disconnected from the patient after eight hours. The data recorder is connected to a customized PC workstation for transfer of the acquired images.

Both capsules now have a real time viewing device that can be plugged into the recorder, but the utility of real-time imaging remains to be elucidated. It may be helpful in deploying capsules and choosing a prokinetic or purgative to improve completion rates depending on capsule location [13,14].

**Indications**

The original PillCam SB was approved for visualization of the small bowel in children and adults aged 10 and older [15-18]. It was then used successfully in children as young as 3 with endoscopic placement [19]. The PillCam and AGILE system are now approved for children older than 2 years [20].

**Obscure GI Bleed/Iron Deficiency Anemia**

Capsule endoscopy has most commonly been used to evaluate for obscure GI Bleed (OGIB), including iron deficiency anemia. A large meta-analysis involving 22,840 capsules, 66% were done for obscure GI bleed. In this subset, the detection rate was 61 percent [21]. In 2006, the American Society for Gastrointestinal Endoscopy Technology Assessment Committee concluded that for OGIB, capsule endoscopy was superior to both push enteroscopy and radiologic studies [22]. Literature supports the use of video capsule endoscopy in the setting of unexplained iron deficiency and has proven to be superior to CT-enteroclysis in endoscopy and small bowel follow through negative findings, and serology. Capsule endoscopy may be helpful in

**Crohn’s Disease (CD)**

Crohn’s disease is established by a combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings, and serology. Capsule endoscopy may be helpful in diagnosing patients with symptoms suggestive of Crohn’s disease or indeterminate colitis. Many studies have attempted to assess the value of capsule endoscopy and a consensus still has not been reached [29-36]. Before capsule endoscopy should be undertaken, evaluation should be done in any patient with known or suspected strictures with either small bowel imaging or a patency study. Capsule retention is as high as five percent even after performing an initial small bowel study [37]. Capsule endoscopy has been found to be superior to all other radiologic imaging modalities in detecting mucosal abnormalities in nonstricturing CD, [38-40] but has much higher diagnostic yield when performed in patients who have abdominal pain or diarrhea PLUS abnormal imaging, inflammatory markers or extraintestinal manifestations [37,38,41]. This is complicated by the lack of validated criteria to diagnose CD. The most common lesions seen are aphthous ulcers and erosions which can look similar to NSAID induced erosions. NSAIDS should be held at least 30 days before evaluation [42,43]. This is also limited by 13.8% of patients who are asymptomatic and not on NSAIDS will have mucosal breaks and other lesions on capsule endoscopy [44]. Current proposed number of lesions to be significant in absence of NSAIDS ranges from more than 3 to more than 10 [45,46]. The value of other findings such as villous edema, villous denudation, erythema, vasculitis, cobblestone appearance, nodular lymphoid hyperplasia, lymphangiectasia or strictures remains unclear. More follow-up studies are needed to validate these findings. The value of capsule endoscopy in monitoring mucosal healing remains debatable, [47,48] as does post-surgical recurrence. Multiple activity indexes have also been developed to assess severity in Crohn’s disease, but none have been independently validated or compared against each other [49-51].

**Small Bowel Tumors**

Capsule endoscopy has a role in the diagnosis and evaluation of small bowel tumors. Benefits have been suggested in the surveillance of the polyposis syndromes [52,53] but another study has found it to be inferior to push enteroscopy and lower endoscopy in familial adenomatous polyposis. Small bowel tumors are occasionally found in the evaluation of obscure GI bleed, abdominal pain, and diarrhea. In a large study of 29 centers in 10 European countries, 5129 patients underwent VCE. 124 (2.4%) had small-bowel tumors (112 primary, 12 metastatic). Among these patients, indications for VCE were: obscure gastrointestinal bleeding (108 patients), abdominal pain (9), search for primary neoplasm (6), diarrhea with malabsorption (1). The main primary small-bowel tumor type was gastrointestinal stromal tumor (GIST) (32%) followed by adenocarcinoma (20%) and carcinoid (15%); 66% of secondary small-bowel tumors were melanomas. Of the tumors, 80.6% were identified solely on the basis of VCE findings [54].

Another review at 14 centers throughout Korea evaluated 1332 cases undergoing CE with all clinical indications. Small bowel tumors were diagnosed with CE in 57 (4.3%) of 1332 patients. The tumors were malignant in 33 cases, and included three adenocarcinomas, eight lymphomas, 20 gastrointestinal stromal tumors, and two metastatic cancers. The most frequent indications for capsule endoscopy in malignant tumors were obscure gastrointestinal bleeding, followed by abdominal pain and weight loss. Thirty of 57 tumors were found exclusively by capsule endoscopy and they were smaller in size compared to the other tumors detected in radiological studies [55].

**Celiac Disease**

Celiac disease is a gluten-dependent enteropathy, characterized by chronic small bowel inflammation and mucosal atrophy. Video capsule endoscopy has an 8-fold magnification capacity lens optical system that allows a magnification similar to that of dissection microscopy and provides a way to evaluate patients unwilling or unable to undergo EGD [56].

Duodenal biopsy remains the gold standard. No standard interpretation of small bowel findings exists but multiple studies have been promising [57-61]. The sensitivity, specificity, positive predictive value and negative predictive value for capsule endoscopy in recognizing villous atrophy were 85%, 100%, 100% and 88.9%, respectively [59]. Using duodenal histology as a gold standard, another study found good sensitivity (87.5%) and specificity (90.9%) for the detection of villous atrophy [61]. Capsule endoscopy has been shown promise in the monitoring of type II refractory celiac disease for ulcerative jejunitis and intestinal T-cell lymphoma, but larger studies are needed [62]. Capsule endoscopy may also be useful in complicated disease. In a series of 47 celiac patients with a high risk of complication (persistent unexplained abdominal pain, weight loss, history of small bowel neoplasia, long-standing celiac disease, positive fecal occult blood
test or iron deficiency anemia unresponsive to iron supplementation), lesions were detected in about 50% of cases [63].

Contraindications

Absolute contraindications

The only absolute contraindications to video capsule endoscopy are pregnancy and small bowel obstruction, pseudoobstruction, or fistula. Pacemakers and cardiac defibrillators are still listed as a contraindication due to concerns over electromagnetic interference, but no reports of failure or interference has been reported [64-67].

Relative contraindications: Stricture

If concern exists about stricture or adhesions due to inflammatory bowel disease or previous history of obstruction, abdominal surgery, radiation or suggestive imaging, the AGILE Patency System (Given Imaging Ltd, Yooqneam, Israel) may be employed. This is the same size as the PillCam video capsule, is dissolvable and biodegradable, and has a lactose body with 10% barium to enable fluoroscopy visualization. It also contains a Radio Frequency Identification (RFID) tag to determine capsule location. Evaluation to see if the capsule is still in the bowel occurs 30 hours post ingestion. If the capsule fails to pass, it will dissolve in the bowel. Early studies appear promising that if the AGILE capsule is passed through the gut, patency is assured and wireless video capsule endoscopy is considered safe [68-70].

Relative contraindications: Aspiration

High risk for aspiration, dysphagia, or esophageal stricture may also be a relative contraindication. This can be circumvented with endoscopic placement of the capsule. Two systems have been developed. The AdvanCE capsule endoscopy delivery service (US Endoscopy) has been studied and has been used safely [71]. The PillCamExpress (Given Imaging Ltd, Yooqneam, Israel) is a video capsule delivery device for patients who are unable to ingest the capsule or who have slow gastric emptying times. This was unveiled in San Antonio, Texas, at the ACG conference in October 2010.

Risks

Capsule Retention

Capsule retention has been defined as the capsule remaining in the digestive tract for a minimum of 2 weeks or one that has required directed therapy to aid its passage. Patients at higher risk include those with known Crohn’s disease, radiation enteritis, intermittent small bowel obstruction, severe motility disorders or Zenker’s diverticulum [3]. Overall retention in a meta-analysis of 22,840 procedures was 1.4%. Long-term retention is always related to underlying pathology with the most common cause being due to Crohn’s disease [72]. Rate of retention increases in patients with known Crohn’s disease or small bowel tumors [73,74]. Capsules may be removed surgically or through endoscopy. The development of double-balloon endoscopy is likely causing the amount of surgical interventions to decrease. However, if the capsule if retained, surgery is often required to fix the cause of retention [75].

Limitations

Limitations inherent to video capsule endoscopy are that the capsule cannot be controlled, biopsies cannot be taken, and therapy cannot be delivered. This will have to be overcome with advances in technology. Capsule endoscopy has other limitations which studies have focused on trying to improve.

Poor visualization

Poor visualization is a limitation. No standard bowel preparation or timing has been determined and many bowel preparations have been examined. Results have been mixed. Purgatives appear to be of likely benefit [10-12]. Simethicone has been found to decrease intraluminal air bubbles and improve mucosal visibility, [79,80] but has also been shown to be inferior to magnesium citrate in grading of mucosal visibility [81].

Incomplete examination

Incomplete examination occurs most often due to the battery failing before passage of the capsule into the cecum. Battery life is currently limited to eight hours, which causes 17% to 25% of examinations of the small bowel to be incomplete [1,2].

Potential areas that have been examined include patient positioning and prokinetics. As the capsule transverses the small bowel, images are captured at 2 frames per second; too fast a passage could cause lesions to be missed. Hence, there has been a focus on trying to improve transit time through the esophagus and stomach in many studies to maximize time in the intestines. No patient position has been found to be superior. An initial study showed promise that placing the patient in the right lateral position was beneficial, [82] but further study has not supported this as it influences gastric transit time not rate of VCE completion [83].

Studies of prokinetics have been mixed. Oral erythromycin was not found to be helpful to increase cecal completion rate [84]. Mosapride and metoclopramide may increase cecal completion rate [85,86]. Lubiprostone and bisacodyl has not been found to be helpful [87,88]. Prokinetics and purgatives were recently evaluated in a randomized controlled trial evaluating simethicone, metoclopramide, Citromag, senna and combinations of the drugs. Completion rates were not improved in any combination of preparation [89]. A trial of gum chewing has shown benefit in cecal completion rate [90].

Future Applications

Capsule endoscopy has classically been used as a method to evaluate the small bowel, but studies have found that significant lesions are also seen in the stomach and colon, despite poor preparation often seen [91-93]. A retrospective study examining 87 patients found colonic findings in 9.1% of patients, [91] while another found 5 colon lesions in 140 patients [92]. Not too surprising then, other modalities to evaluate the stomach and colon are being developed. There may also be utility in using capsule endoscopy for evaluation and monitoring of esophageal varices.

New Capsules

PillCam SB 2-EX (Given Imaging Ltd, Yooqneam, Israel) is a small bowel capsule which extends capsule operating time to a minimum of 12 hours for patients who are confirmed or believed to have slow motility. This was introduced at ACG in San Antonio in October 2010.

The Pillcam COLON capsule endoscopy (Given Imaging Ltd, Yooqneam, Israel) has also shown promising results as a new modality to evaluate for colorectal cancer screening [94-101]. It is in clinical trials in Europe. This dual camera capsule acquires pictures from both ends at the rate of four frames per second. A study evaluating 36 patients who underwent colon capsule endoscopy followed by conventional colonoscopy found that 7/11 polyps detected by colonoscopy were found by the capsule. Conversely, one polyp seen on colon capsule endoscopy was not seen in colonoscopy. Visualization of the rectum...
was also difficult on colon capsule endoscopy due to poor cleanliness [94].

Preparation for colon capsule endoscopy (CCE) is not only important for visualization, but is also important for propulsion of the capsule. If the goal is to perform colonoscopy on patients who have findings on CCE, then the capsule must pass through the body in an acceptable time frame. In the above study, the addition of sodium phosphate resulted in a mean total transit time of 4.6 +/- 1.9 hours with colon transit time of 96 +/- 66min. If sodium phosphate was omitted and replaced with extra polyethylene glycol, the mean total transit time was 8.3 +/- 1.6h and colon transit time was 303 +/- 134min [94]. The necessity of a sodium phosphate booster was further validated in a subsequent trial [95]. At this time, sodium phosphate is not recommended in the United States due to kidney related complications.

A PillCam COLON2 has already been developed. The angle of view has been widened from 154° to 172° for each camera, thus offering a panoramic view. The recorder was also upgraded. This new recorder is equipped with artificial intelligence and is turned into an active participant of the study and can communicate and execute orders with the capsule. This recorder has an Adaptive Frame Rate (AFR), which adjusts the image capture rate from 4 frames per second (fps) to 35 fps, based on capsule movement. Studies are ongoing.

Other Areas of Interest

Both FDA approved capsules have plug in devices that permit real time viewing. A recent study has evaluated this in the emergency room in the setting of acute upper GI bleed with the PillCamEso. Live Viewing enabled the identification of high and low risk patients and was able to risk stratify the patients who needed EGD in under six hours versus twenty-four hours [102].

Dual camera capsule technology is now available with the Pillcam Colon capsule endoscopy. Use of this capsule in the small bowel shows the dual cameras appear to complement each other and detects smaller bowel lesions [103].

VCE may also have a complementary role with PET-CT in evaluation of small bowel metastasis in melanoma and further studies will have to be performed to validate this finding [104].

Conclusion

In summary, video capsule endoscopy has evolved tremendously over the last decade, and will likely make substantial advances in the near future. As technology improves, a capsule will likely be developed that can evaluate the GI tract from mouth to anus, with sufficient battery life and the ability to sample and provide therapy to lesions. Further advancements will expand and diversify indications for video capsule investigation.

References

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