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Crohn's Disease: A Comparative Study on the Noninvasive Diagnostic Methods for Small Bowel Disease

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Abstract

The non-invasive methods used in the diagnosis of small bowel disease includes; Capsule Endoscopy, Double Balloon Enteroscopy, Single Bowel Enteroscopy, Computed Tomographic Enterography, Magnetic Enterography, Small Bowel Follow Through and Small Intestine Contrast Ultrasonography. These techniques have been useful in detection of suspected and established Crohn's disease, mucosal lesions, extraluminal extensions, fistula, abscesses, fistulas etc. The objective of this research was to compare the non-invasive techniques used for diagnosis of Crohn's disease with the aim of proposing the most preferred. MEDLINE, EMBASE and Cochrane databases were searched for studies involving non-invasive diagnostic method for CD. Different diagnostic techniques were analyzed and compared for parameter such as specificity, sensitivity and detection of complication. It was concluded that Small Intestine Contrast Ultrasonography (SICUS) was the most preferred technique with the sensitivity of 97.5% and specificity of 100%. In addition, SICUS showed high accuracy for detection of complications in the small intestine in comparison to other diagnostic modalities.

Keywords: Crohn's disease; Diagnostic methods; Small bowel disease; Small intestine contrast ultrasonography; Capsule endoscopy; Double balloon enteroscopy; Single bowel enteroscopy; Computed tomographic enterography; Magnetic enterography; Small bowel follow through; All Saints University School of Medicine; Dominica; Meta-analysis.

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1. Introduction

The diagnosis of small bowel Crohn' disease (CD) has evolved from invasive and expensive procedures such as ileocolonoscopy (IC), to noninvasive radiologic procedures including small bowel follow through (SBFT), small bowel enteroclysis (SBE), computed tomographic (CT) Enterography Magnetic resonance (MR) Enterography, Video capsule endoscopy (CE), Double Balloon enteroscopy (DBE), single balloon enteroscopy (SBE), contrast radiology, Transabdominal ultrasound (TUS), small intestine contrast ultrasound (SICUS) and spiral enteroscopy [1,2].

The SBFT examination is the standard radiological technique used to diagnose patients with active CD as around 70% of patients have involvement of the small intestine [3,4]. However, small bowel studies have shown SBE to be more accurate than SBFT in diagnosing active CD by detecting early mucosal lesions [5,6,7]. In regard to the state of the bowel wall and extraluminal extension of CD both methods provide only limited and indirect information [8,9,10]. In addition, these methods are disadvantaged by overlapping bowel loops [6, 11, 12].

Patients with CD are often young and suffer from chronic and relapsing episodes of CD for which they have to undergo repeated imaging examinations to assess the status of their disease. SBFT and SBE have been widely used for diagnosing lesions located in the small bowel, but are now being replaced by CT Enterography [10,13]. CT Enterography procedure is considered more accurate in diagnosing CD by detecting inflammation of the entire wall and also, the complications associated with it such as strictures, abscess and fistula formation. However, CT Enterography procedure is avoided in children and women of child bearing age due to the risk involved with over exposure of harmful radiation [14-16].

Magnetic resonance imaging (MRI), Contrast radiology, CT and TUS are also used widely for diagnosing CD lesions of the SB and of strictures, abscesses, and fistulas which complicate CD [8, 17, 18, 19, 20, 21, 22]. MR Enterography is a radiation-free alternative method to assess patients with CD. The use of MR Enterography in evaluation of extraenteric complications has been shown by several reports in patients with CD in identification of active ileitis [23]. MR Enterography along with ultrasound are considered as investigation of choice for other small bowel diseases such as irritable bowel disease [24, 25, 26]. MR Enterography is more sensitive than CT imaging and is the preferred modality in evaluating small bowel CD [24]. However, it is disadvantaged due to time, cost, and less availability in many centers [27]. Recent reports have shown that CT, MRI, and ultrasounds are superior to the common radiographic procedures (SBFT, SBE) for the detection of CD due to their high diagnostic accuracy and better definition of the extraluminal inflammatory involvement [28-31]. This justifies the reduced use of traditional radiologic assessment worldwide [15]. The evaluation of CD by CT Enterography has been accepted as a noninvasive imaging technique [5, 6, 10, 32]. CT Enterography with the use of oral neutral contrast agents and rapid intravenous contrast infusion can be used to identify inflammation in the small intestine, allowing direct visualization of extraenteric structures [5, 6].

The ingestion of an intraluminal oral contrast before abdominal ultrasonography helps to visualize the entire small bowel and is comparable to radiology in detection of site, number, and length of SB lesions in patients

with diagnosed and undiagnosed SB cases [33-36]. When diagnosing small bowel lesions and complications of CD, conventional ultrasound might be disadvantageous in visualizing pathology due to presence of gases with the GI tract [37-39]. The administration of oral contrast before performing abdominal ultrasound allows bowel loop distension, thereby facilitating the visualization of the bowel wall and improving discrimination between adjacent intestinal loops [40]. SICUS has shown increased overall sensitivity in detecting lesions along the entire length of the small bowel in CD cases, from 57–96% (conventional ultrasound) to 96–100% [36, 35, 41, 42]. In all, the detection of suspected and established Crohn's lesions with SICUS has shown a sensitivity and specificity surpassing 95% when compared with SBFT and SBE and connects well with CT Enterography [35, 36, 43, 44].

CE has also shown to play major role in the detection small bowel tumor. In addition to being safe and non-invasive, CE can visualize the entire small bowel and has been proved by studies better than enteroscopy, CT and SBFT in detection of small bowel bleeding lesions [45-47]. The increased detection of small-bowel has been important for histopathological confirmation of disease by CE in device-assisted enteroscopy, thereby, enabling endoscopic therapy in selected cases and thus avoiding the need for surgery [48, 49]. The Food and Drug Administration have currently approved the use of CE in the United States for adult and pediatric patients over 10 years of age for CD, in detection of small bowel abnormalities [50].

Hence, the objective of this project is to compare a number of these non-invasive techniques used for small bowel disease with the aim of proposing the most preferred one.

2. Materials and method

The research was a systematic review with meta-analysis conducted by analyzing previous studies obtained from MEDLINE, EMBASE and Cochrane databases involving any non-invasive diagnostic method for CD. Noninvasive methods include: Small Bowel Follow Through (SBFT), Computed Tomographic Enterography, Magnetic Enterography, Video Capsule Endoscopy (CE), Double Balloon Enteroscopy (DBE), Single Balloon Enteroscopy (SBE), Contrast Radiology, Small Intestine Contrast Ultrasound (SICUS) and Spiral Enteroscopy.

Video CE involves swallowing a video capsule after an 8- to 12-hour fast, peristalsis then carries the capsule through the gastrointestinal tract. Capsule can be delivered with endoscopic assistance or is swallowed by the patient. The tiny capsule is propelled by peristalsis, and has an imaging capacity of two frames per second over 8 hours. Digital images of the GI tract mucosa are recorded and transmitted by the UHF band radio to a data recorder around the patient's waist. Images that contain blood are marked for closer examination.

Balloon assisted enteroscopy **(**BAE) are of two types: double balloon and single balloon enteroscopy. This procedure requires deeper intubation. SBE entails insufflation of intestine with CO_2 and sedation with propofol or general anesthesia before start of the procedure. This procedure involves passing the enteroscope through the esophagus (anterograde approach) to the duodenum till it can no longer advance forward, then the overtube which has an inflatable balloon fixed to the distal, radiopaque tip is pushed in over the enteroscope. The inflated balloon, the overtube and the endoscope are pulled to shorten the intestine and to advance into the small bowel.

The maneuvers is repeated to permit more advancement through the bowel. DBE is similar to SBE. DBE has latex balloons attached to both the overtube and the endoscope unlike the SBE. The balloons are inflated and deflated during insertion. Friction at the intestinal wall and enteroscope interface enables the small bowel to be pushed back to the overtube. The enterescope balloon is then deflated after the overtube balloon is deployed. The process is then continued until the entire small bowel is visualized. Retrograde approach can also be used, this entails going through the colon and into the ileum to view the distal part of the small bowel.

CT Enterography involves the use of Computer Tomographic scan. Prior to the procedure, the patient is kept nil per oral for 5hours and the abdomen is distended which prevent pathology mimicry. The contrast (positive or negative) is then administered to patient and CT Scan is performed. Axial and Coronal reformatted images are used for proper evaluation of results.

MR Enterography entails drinking mannitol solution which acts a hyperosmolar agent which draws fluid into the bowel. Patient should not eat or drink 4-6 hours before the examination. Scanning is performed on a 1.5-t MRI scanner either in supine or prone position.

In spiral enteroscopy, the overtube device is lubricated and placed over the enteroscope and locked at the collar. The enteroscope is carefully inserted into the esophagus with the patient lying on the left side and then advanced to the ligament of Treitz. The locking device is then loosened and the enteroscope is further pushed. The overtube is then pushed towards the tip of the enteroscope and re-engaged, then the small bowel is pleated onto the overtube rotating it in a clockwise direction. Finally, the collar is disengaged and the enteroscope is advanced as further as possible to add depth of small bowel intubation. The overtube handles are then rotated in a counterclockwise direction and the mucosa gets 'released' in a controlled way which allows a marked evaluation of the small bowel wall.

SBFT is a fluoroscopic technique that obtains high resolution images of the small bowel. It is a single contrast study (oral contrast): either barium or water soluble contrast. It is often done after an upper GI fluoroscopic study, as the contrast column moves from the stomach and duodenum to the small bowel.

3. Results

The result obtained from meta-analysis of past studies was compared for different procedures in diagnosing CD, with emphasis laid on the non-invasive methods (Table 1).

In a study carried out on the importance of alternative diagnostic modalities in the diagnosis of small bowel tumors after a negative capsule endoscopy, it was shown that capsule endoscopy may overlook important risky lesions. The study highlights the significance of using modified diagnostic methods after a negative capsule endoscopy, more importantly in patients with a high risk of small bowel tumor pathology or persistent or recurrent bleeding. There was evaluation of 223 patients with non stricturing CD by carrying out 11 prospective studies which involved comparison of CE with SBFT, IC, PE and CT Enterography in patients with suspected or diagnosed with CD. Compared with other methods, CE had a remarkable yield of 15 – 40 %, especially in patients established with CD. In further analysis by the same researchers it was suggested that CE has a higher

outcome than SBFT even in patients suspected with CD. A four-way comparison trial found sensitivity of 83%, 83%, 74%, and 65%, respectively in CE, computed tomography Enterography, IC, and SBFT. In comparison, CE showed a specificity of 53% which was significantly lower. Studies also revealed that, CE demonstrated diagnostic yields of 39 % in detection of established disease and 13 % for findings suspected CD which was quite comparable to that of IC.

Table 1: Source and their associated findings/result

SOURCE	**FINDINGS**
Ribeiro and his colleagues, 2015	DBE, CT Enterography, are diagnostic for CE negative results.
Triester *and his colleagues*, 2006	CE showed incremental yield when compare with IC, SBFT, CT Enterography.
Dionisio *and his colleagues*, 2007	CE showed higher yield than SBFT.
Solem *and his colleagues*, 2008	CE showed lower specificity than other methods.
Mehdizadeh *and his colleagues*, 2010	CE showed diagnostic and predictive yield.
Lee *and his colleagues*, 2009	MR Enterography showed to be radiation free alternative for CD as opposed CT.
Hassan *and his colleagues*, 2009	CT showed a better image quality as opposed MRI.
May *and his colleagues*, 2010	DBE showed a complete enteroscopy three times that of SBE.
Castiglone *and his colleagues*, 2013	MR is sensitive in defining extensions as opposed bowel sonography (BS).
Pallotta *and his colleagues*, 2012	SICUS is accurate for detection for small intestine complications.
Kumar *and his colleagues*, 2014	SICUS identified small bowel complications and correlated with MR Enterography.

In a prospective comparison of "State of the Art" MR Enterography and CT Enterography in Small Bowel Crohn's Disease**,** 33 patients underwent CT and IC, out of which 30 also underwent MRE. There was similarity in the sensitivities of MR Enterography and CT Enterography (90.5% vs 95.2%, respectively; $p = 0.32$) for detecting active small-bowel CD. CT Enterography had a higher image quality scores ($p = 0.005$) than MR Enterography examinations. 8 cases (24%) with small-bowel inflammation were identified using MR Enterography and CT Enterography in which the ileal mucosa previously appeared normal at IC. In addition, Enterography provided the imaging in three additional patients who did not have ileal intubation.

In a Prospective Multicenter Trial Comparing Push-and- Pull Enteroscopy with the SBE and DBE techniques in patients with small bowel disease, there was relative lesser time in preparing SBE as compared to DBE ($P <$

0.0001). It was observed that DBE technique achieved complete enteroscopy in 66 % of cases (33 patients), either with the oral route alone or with combined oral and anal approaches. SBE technique, however with respect to complete enteroscopy rate was significantly lower at 22 % ($P < 0.0001$; 11 patients, only with oral and anal routes combined).

Another study carried out to evaluate Noninvasive Diagnosis of CD involved direct comparison of bowel sonography (BS) and MR Enterography in which the diagnosis of small bowel CD was made in 120 of 249 subjects (48%). CD diagnosis with BS revealed the sensitivity of 94%, specificity 97%, positive predictive value 97%, and negative predictive value 94%. On the other hand, MR Enterography showed sensitivity 96%, specificity 94%, positive predictive value 94%, and negative predictive value 96%. MR Enterography was more accurate in demonstrating the length of CD than BS, whereas, in terms of CD localization, the correlation between the two procedures were high. Also, MR Enterography showed a fair concordance with BS about strictures (k ¼ 0.82) and abscesses (k ¼ 0.88), with better detection of enteroenteric fistulas (k ¼ 0.67).

In a prospective Comparative Study Versus Intraoperative Findings, SICUS was evaluated for the detection of Small Bowel complications in CD. At least one stricture was identified with SICUS excluding it in 9/9 (97.5% sensitivity, 100% specificity, k ¼ 0.93); 9/12 in two or more strictures (75% sensitivity, 100% specificity, k ¼ 0.78). K-statistics showed the agreement between SICUS and surgery in identification of proximal and distal site in small intestine stricture was 1 and 0.92, respectively.

In a study carried out to correlate the intraoperative findings and MR Enterography with SICUS for the detection of small bowel complications in Crohn's disease, 67 patients were evaluated; SICUS was carried out in 25 patients and 17 patients underwent MR Enterography before surgery. Another 25 patients underwent both SICUS and MRE. When compared with intraoperative findings, the sensitivity of SICUS was 87.5% and MR Enterography was 100% in detecting strictures, 87.7% and 66.7% for detecting fistulae, 100% for both in identifying abscesses, 100% and 66.7% for detecting bowel dilatation, and 94.7% and 81.8% in defining bowel wall thickening, respectively. The correlation for SICUS and MR Enterography with surgery, showed a high level of agreement in localizing strictures ($\kappa = 0.75, 0.88$, respectively), fistulae ($\kappa = 0.82, 0.79$) and abscesses ($\kappa = 0.87, 0.77$). Correlation between SICUS and MR Enterography was remarkable or almost same in identifying strictures ($\kappa = 0.84$), with number and location ($\kappa = 0.85$), fistulae ($\kappa = 0.65$), and mucosal thickening ($\kappa = 0.61$) .

4. Discussion

The paucity of a non-surgical gold standard for comparison has made diagnostic studies for small bowel diseases more difficult. Assuming that the most sensitive method should set the "standard" may be incorrect due to unrecognized false positive results [51].

The results of this study show that all diagnostic methods are reliable in detecting and accessing small bowel complications in CD. The least sensitivity of all diagnostic method was SBFT with sensitivity of 65%. SICUS had the highest sensitivity of 97.5% and specificity of 100%. Another advantage of SICUS is the real-time

evaluation of bowel wall for not just anatomical but also functional abnormalities [52]. SICUS and transabdominal ultrasound are cheaper, easy to use radiographic techniques with high availability and has shown good tolerance by children as they are radiation free [53]. They can be performed without sedation and with little preparation. SICUS has demonstrated a high level of accuracy in identifying stricture site, fistula site, and abscesses. SICUS precisely identifies mucosal thickening and bowel dilatation, with sensitivities of 94.7% and 100% respectively [54]. However, the SICUS sensitivity is reported to be significantly lower for less accessible locations such as duodenum/jejunum (28.6 %) and rectum (14.2 %).

MR Enterography is sometime considered as the main standard in small bowel imaging because it accurately assesses extra-luminal diseases such as fistula and strictures, sometimes missed by barium studies. It also has an added benefit of no exposure to medical radiation. MRE and SICUS show close sensitivity and specificity although SICUS had a higher sensitivity when considering the presence of fistula, bowel wall thickening and luminal dilatation [47].

CE has advantages of comfort: no hospitalization, pain and cutting and no anesthesia. CE also affords superior mucosal evaluation compared with most imaging examination. However, CE has multiple disadvantages such as retention of capsule, poor identification of lesion site, equivocal evaluation in the presence of excess luminal fluid. Unlike standard endoscopy, treatment or biopsy sampling of abnormalities, manipulating the camera orientation to evaluate the abnormality further or cleansing of poorly prepared areas, can't be done with capsule endoscopy. Also, the quality of images in capsule endoscopy is lower than standard endoscopy. CE contraindications include small bowel stricture or obstruction, pregnancy and in patients using pacemakers [55]. Results showed that CE in comparison with CT Enterography, IC, and SBFT had a sensitivity of 83%, 83%, 74%, and 65%, respectively. CE is superior to these methods but still of less sensitivity to SICUS (97.5%) and MRE (96%) and far less specificity of 53% to SICUS and MRE (100% and 94% respectively) [56].

CT Enterography and MR Enterography showed similar sensitivities (95.2% vs 90.5% respectively for detecting active small-bowel Crohn's disease) [57]. CT Enterography has numerous advantages over SBFT and conventional enteroclysis such as inspection of the entire small bowel, demonstration of extraluminal pathology in addition to luminal disease, unhinderance by overlapping loops and increasing diagnostic accuracy. Therefore, a single CT Enterography may eliminate the necessity for multiple radiological tests, thus improving diagnostic efficiency while saving cost, increasing patient compliance and reducing radiation exposure [58].

SBFT has shown the advantage of achieving good mucosal detail and the distension achieved with enteroclysis improves the visualization of fistulas, mural or intraluminal filling defects such as small bowel neoplasms and sites of small bowel obstruction [59]. But SBFT has showed sensitivity of 65% which is the lowest in this study. Barium studies have shown limited role in the diagnosis of acute small bowel obstruction and in the evaluation of extraluminal disease, and patients are almost often referred for additional CT studies to characterize the small bowel lesions. There's also the disadvantage of exposure to radiation which is of greater implication when a young patient is involved.

Results showed that it took lesser time to prepare SBE than DBE but DBE achieved superior complete

enteroscopy (66% DBE vs 22% SBE) and higher diagnostic yield. The insertion depth reached with the SBE technique is usually lower than with the DBE technique which equally results in a lower diagnostic yield. Advantages of DBE over SBFT, wireless CE and push enteroscopy includes: visualization of the entire small bowel till the terminal ileum, application of therapeutics, biopsy of small bowel mucosa, small bowel polyp resection and the placement of stents or dilatation of strictures [60]. Main disadvantage is the long time required to visualize the small bowel which can exceed three hours, and may require the patient to be admitted in the hospital. Also, cases of acute pancreatitis and intestinal necrosis have been reported to be associated with the technique [61].

5. Conclusion

Ultimately, more prospective studies are needed to determine the role of CE in evaluating suspected and established CD and influencing clinical outcomes. CE and DBE have similar yield for Crohn's disease diagnosis and are complementary. CE is of advantage because it has a higher rate of success for achieving total enteroscopy and it is noninvasive, whereas balloon assisted enteroscopy is useful for tissue diagnosis. Balloon assisted enteroscopy can also be used for therapeutic interventions in CD. DBE is useful in facilitating endoscopic dilation of Small bowel strictures, reducing the need for surgery and it is also used to retrieve retained capsules, which also helps avoid surgery [62].

In conclusion, SICUS should be the first choice examination in patients with suspected CD and should also be performed prior to endoscopy. While MR Enterography is the first line of investigation for small bowel in patient with known CD, as it is a well-tolerated examination, with advantages of minimal exposure to radiation. SICUS and MRE can be used for children as there is no risk of radiation exposure. CT should be restricted to cases where MRI is contraindicated, in emergency situations when ultrasound is inadequate or for non-cooperative younger children. SBFT seems to be widely replaced by MR Enterography in the population, despite its lower cost. However, SBFT currently has a questionable role because of its low sensitivity and barium exposure, therefore, should be only used when MR or CT Enterography are unavailable [63].

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