CAPSULAR ENDOSCOPY: A SINGLE CENTRE EXPERIENCE

By

Nisholini Naicker

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As the candidate's supervisor I have approved this thesis for submission.

Signed: [redacted] Name: Bilkish Cassim_____ Date: 01.09.2021____

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I, Nisholini Naicker, declare that

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Abstract

Background: Capsule endoscopy (CE) is a relatively new modality in the assessment of obscure occult and obscure overt gastroenterological (GI) bleeding in South Africa.

Objectives: The aim of this study was to describe the indications, findings and outcomes of CE at a referral hospital in the public sector in Kwa-Zulu Natal (KZN).

Methods: Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of Kwa-Zulu Natal (UKZN). A retrospective electronic chart review of 27 subjects who underwent CE from its introduction in 2013 to 2018 was undertaken. A structured data sheet was used to extract demographic and clinical details and the endoscopist's report.

Indications were classified as obscure occult GI bleeding, obscure overt GI bleeding, suspected Crohn's disease and unexplained macrocytic anaemia (in a single subject).

The findings at endoscopy were categorised as vascular (angiodysplasia, varices), inflammatory (villous oedema, erythematous mucosa erosions, ulcers or stenosis), normal, inconclusive or other (villous atrophy, polyps, tumours).

Results: The mean age of the 27 patients was 51.2 years ± 21.3 years, with a majority of women (15, 56%) and 12 (44.4%) men. The most common indications for CE were either obscure occult GI bleeding or obscure overt GI bleeding. One patient each had unexplained anaemia and suspected Crohn's disease. All subjects had had previous oesophagogastroduodenoscopy (OGD) and colonoscopy prior to the CE, 15 subjects (55.5%) had had a CT scan of the abdomen and seven (26%) underwent red cell scans.

Of the 14 subjects with occult GI bleeding, 12 had severe iron deficiency anaemia, with symptom duration ranging from one year to 40 years. These subjects had undergone a minimum of one up to a maximum of six OGDs, with a total of 38 OGDs prior to CE. Abnormal findings on CE were reported in nine subjects (64.3%), the commonest of which was inflammatory, and a definitive diagnosis was made in six (42.9%) subjects.

The 11 subjects with obscure overt GI bleeding had undergone a total of 27 prior OGDs prior to CE. Abnormal findings on CE were reported in three of the 11 subjects (27.3%) with obscure overt GI bleeding and a definitive diagnosis made in two subjects (18%).

In addition, the diagnosis was supported in the patient with Crohn's disease who had been symptomatic for eight years and had had several previous OGDs and colonoscopies.

In the total group who underwent CE, nine (33.3%) subjects attained a definitive diagnosis. A further 18.5% attained a diagnosis following subsequent investigations. In three subjects (11.1%) the initial indication resolved requiring no further therapy or investigation and two patients (7.4%) were lost to follow up.

Capsule retention occurred in two patients and the capsule was successfully retrieved via laparoscopic surgery.

Conclusion: Capsule endoscopy is a useful modality to further investigate select patients with unexplained GI bleeding, including the identification of lesions outside the small bowel. A guideline for the application of CE in the South African context is required.

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Abbreviations

OGD- Oesophagogastroduodenoscopy

CT- Computerised Tomography

CE- Capsule Endoscopy

ESGE- European Society of Gastrointestinal Endoscopy

M2A- Mouth to Anus

VCE- Video Capsule Endoscopy

WCE- Wireless Capsule Endoscopy

OGIB- Obscure Gastrointestinal Bleeding

USA- United States of America

MRI- Magnetic Resonance Imaging

HHT- Hereditary Haemorrhagic Telangiectasia

CMUSE- Cryptogenic Multifocal Ulcerous Stenosing Enteritis

KZN- KwaZulu-Natal

IALCH- Inkosi Albert Luthuli Central Hospital

Chapter 1: Literature Review

1. Introduction

Gastrointestinal bleeding is a common condition and in the majority of patients, the site of bleeding can be identified by traditional, luminal endoscopies. In a smaller proportion, bleeding may be obscure. These patients may present with iron deficiency anaemia or positive faecal occult blood testing. Oesophagogastroduodenoscopy (OGD) and colonoscopy may not be helpful, particularly if the causative lesion is in the small bowel. The small intestine is relatively inaccessible compared to the stomach and large intestine. The length of the small intestine, in addition to its free intra peritoneal location, contractility and overlying loops, confounds traditional diagnostic techniques such as small bowel enema, computerised tomography (CT) scans, push enteroscopy, angiography, and technetium 99m labelled red blood scans.

While small bowel barium series have long been considered the mainstay in the evaluation of the small intestine, they have a poor diagnostic yield of 0-5.6% in the investigation of patients with occult bleeding or iron deficiency (1, 2). Consequently, these patients undergo more diagnostic procedures, require more blood transfusions and have a longer hospitalization with higher healthcare expenditure (1).

Capsule endoscopy (CE), first introduced in 2001 to improve the imaging of the gastrointestinal tract and assist in the diagnosis of small bowel pathology (1), has a high diagnostic usefulness and is superior to most traditional diagnostic techniques. Studies have shown an increased detection rate of small bowel pathology by the capsule with a sensitivity of 95% and specificity of 75% (2). Although CE has a good safety profile, an important complication of CE is capsule retention and rarely, capsule aspiration has been described.

The European Society of Gastrointestinal Endoscopy (ESGE) Clinical guidelines recommend the use of CE in patients with obscure gastrointestinal bleeding, Crohn's disease, coeliac disease and small bowel tumours.(2) There have been numerous studies on CE, but only a handful from South Africa. There are no studies from KwaZulu-Natal.

1.1 Capsule endoscopy

Capsule endoscopy is a wireless, ingestible capsule capable of capturing images of the gastrointestinal tract mucosa while being propelled by peristalsis. These images are transmitted wirelessly to a data recorder carried by the patient and later uploaded to a computer where software compiles them into a video for reading. Capsule endoscopy is also known as mouth to anus (M2A), video capsule endoscopy (VCE) and wireless capsule endoscopy (WCE).The exact mechanics of the capsule and the administration and recording process is well described (3). Essentially the patient is asked to swallow the video capsule, which captures images while moving through the bowel. Once excreted, the images are retrieved and the examiner views the video to detect lesions.

Since its introduction in 2001, improvements in technology have led to the development of second and third generation CEs which overcome some limitations of the first generation CE by increasing the view angle, extending the effective battery life, image capture frame rate, and others systems which offer superior image quality, tissue coverage, and interpretation efficiency. Additionally, many real time viewing systems are now available which have enabled application in emergency settings. There are several capsule makes available and they largely yield comparable results in terms of diagnostic yield, image quality and completion rate (1). Currently, trials are underway in innovative capsule designs with advances such as maneuverable capsules, biopsy capacity, extended power source, targeted drug delivery and accurate capsule location (4).

Capsule endoscopy has had a significant impact in broadening the diagnostic yield of small bowel abnormalities because of its unique ability to assess the small bowel in detail. It is primarily used for the evaluation of obscure gastrointestinal bleeding and has found to be useful in diagnosing several clinical conditions including Crohn's disease, coeliac disease, inflammatory bowel disease, and small bowel tumours. Its main advantages being that it is non-invasive, well tolerated, and allows for relatively safe examination of the small bowel with a diagnostic yield superior to radiological investigations (5).

An exact source of bleeding is difficult to establish when the bleeding stops before or during an examination and while possible lesions may be detected, especially if multiple, it is often difficult to identify the main bleeding source.(5) A diagnostic yield, the rate in which the procedure detects what are thought to be significant findings, is often used as a proxy estimate of the diagnostic capability of CE (2). The overall lesion detection rate , the rate at which a positive finding is noted on CE, was reported to be as high as 71.4% (5) with a specificity of 64-94% (6-8). The wide variance in the current diagnostic yield of CE of 38-93% is due to the lack of consensus of the definition of positive findings. In some studies non-specific mucosal changes like red spots, erythema or thickened folds may be considered clinically insignificant, whereas in others, they may be considered to be relevant findings and thus increase the diagnostic yield (9-11).

Accuracy parameters for CE are not truly known because there is no standard comparative method. Furthermore, the indications are heterogeneous and the timing of the CE varies considerably, making it difficult to compare studies. To address this concern, the European Society of Gastrointestinal Endoscopy (ESGE) introduced structured terminology and guidelines for the clinical application of CE (12, 13). The most common indication remains the investigation of obscure gastrointestinal bleeding. Other indications include Crohn's disease, small bowel tumours, inherited polyposis, coeliac disease and miscellaneous indications.

1.1.1 Limitations of capsule endoscopy

The major limitations of CE include a lack of therapeutic opportunities and tissue sampling, and uncontrolled propulsion. Capsule endoscopy relies totally on natural bowel peristalsis therefore the capsule progress is non-steerable, and hence more rapid in the proximal than in

lower segments of the small-bowel. Presently, several research groups are working to design remotely manoeuvrable capsules capable of recognizing lesions and collecting target tissue samples (1).

Procedure and preparation issues are noted to be significant since certain conditions obscure the images such as gastric bubbles, residual food and blood. Evidence suggests that a preparation regimen based on laxatives is more effective than fasting alone in improving the small bowel mucosa visualization (1). It is recommended that patients with delayed bowel movement and constipation fast for longer and drink more water.

Performing CE in the vicinity of telemetric systems can cause interference in the transmission of images to the recorder, resulting in multiple gaps in the videos downloaded. It is therefore recommended to avoid administering the capsule to patients in these vicinities (6).

1.1.2 Indications for capsule endoscopy

1.1.2.1 Gastrointestinal bleeding

Gastrointestinal bleeding is defined as either overt, occult (including iron deficiency), and/or acute or chronic.

Bleeding from a peptic ulcer is a common medical emergency and although most upper gastrointestinal bleeding stop spontaneously, 15-20% continue (14). Despite effective endoscopic diagnostic and therapeutic modalities, upper gastrointestinal tract haemorrhage continues to challenge clinicians (15). Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent gastrointestinal bleeding undetected by endoscopy and colonoscopy. This entity is further described as obscure-overt bleeding, when visible blood is found on further investigation or obscure-occult bleeding, when patients present with either iron deficiency anaemia or positive faecal occult blood testing.

Several studies have defined factors that predict the likelihood of detecting pathology on CE. Specialised indications include acute bleeding, requirement for iron replacement therapy, age over 65 years, male gender, liver disease and use of non-steroidal anti-inflammatory or antithrombotic therapy (16).

Data on accuracy parameters (sensitivity, specificity, positive predictive value, and negative predictive value and likelihood ratios) of CE in OGIB patients are scarce due to the absence of a gold standard and objective criteria for positive findings on CE. Nevertheless, the present evidence on diagnostic usefulness of CE is enough to support the use of CE for OGIB (2, 17, 18).

In a retrospective study of 592 CE procedures performed in a tertiary referral hospital in Amsterdam over a period of 4 years, a diagnostic yield of 49% was reported (12). While Lui et al determined a lesion detection rate of 85.7% for OGIB, the diagnostic rate was only 35.7% (5). The variability in lesion detection and diagnosis is due to the fact that the exact source of bleeding is difficult to establish when bleeding stops prior to or during an

examination. In such cases, even though possible lesions may be detected, if multiple lesions are present the main bleeding source is difficult to determine. When the capsule is administered to patients with on-going overt bleeding, the yield is higher (87-92%) than with previous overt bleeding or iron deficiency anaemia (9). Overall, however in patients with on-going overt OGIB, endoscopy should be considered as first line, given its ability to make a diagnosis and to perform therapy at the same time.

In patients with positive CE, a subsequent endoscopy is usually performed to confirm and treat lesions. A pooled diagnostic yield of endoscopy performed after previously positive CE was 75 % and the odds ratio for the yield of endoscopy performed after a previously positive CE, compared with that of endoscopy performed in all patients was 1.79 (95% CI: 1.09-2.96, P=0.02) (2, 19).

Iron deficiency

Although iron deficiency anaemia is a common indication, it is important that prior to CE a complete medical history (including medication use, comorbidities, and gynaecological history), and an endoscopy with duodenal and gastric biopsies is undertaken (8). Bidirectional endoscopy identifies the cause of iron deficiency in 70-80% of patients (20). When this is negative, then the small bowel requires further investigation (2, 20). In a systematic review pooling data from four studies on iron deficiency anaemia, a diagnostic yield for CE of 66% was reported, which is comparable to previous studies (21).

Acute gastrointestinal haemorrhage

The use of CE in acute gastrointestinal haemorrhage was first reported by Rubin et al who showed that CE could accurately identify high risk and low risk patients and be a useful risk stratification tool to determine the need for therapeutic intervention (22). A modified oesophageal CE, with extended battery life, was demonstrated to be safe and effective in correctly identifying acute gross gastrointestinal bleeding with a sensitivity of 50%, specificity 66%, positive predictive value of 20% and negative predictive value of 89% (23).

Further studies have confirmed the value of CE in the emergency department for patients with acute upper gastrointestinal haemorrhage (23, 24). Furthermore, CE is more accurate than conventional screening tools in correctly predicting high risk and low risk endoscopic stigmata of recent haemorrhage (15). The use of CE as an endoscopic triage tool in patients with suspected acute upper gastrointestinal bleed has also been shown to significantly reduce hospital admissions in low to moderate risk patients and to better identify low risk patients compared to traditional scoring tools (15, 24).

Currently the ESGE recommends emergency CE in patients with on-going overt OGIB. This is based on two retrospective studies and one randomized controlled trial comprising of less than 100 patients overall. Emergency CE performed within 24 to 72 hours from admission during severe on-going overt OGIB appears to be an effective modality with a diagnostic yield up to 70% and has a significant impact on patient management (25-27).

In the United States of America (USA), CE is considered cost effective for low and moderate risk patients presenting with acute upper gastrointestinal haemorrhage, compared to the other strategies since many patients without the need for intervention can be safely discharged home without incurring the costs and potential complications associated with a hospital admission (28).

However, CE may be negative. In 49 patients who underwent CE for OGIB, and in whom CE was negative, a re-bleeding rate of 32.7% was reported (10). Several reviews and consensus recommendations conclude that patients with OGIB and normal CE have a good prognosis with a low risk of re-bleeding and should be managed conservatively with no further investigations (29, 30).

Timing of capsule endoscopy in gastrointestinal bleeding

Earlier CE in patients with OGIB is associated with an increased diagnostic yield compared with late CE (12). Detection rates of up to 92% are seen when CE is performed within 15 days of an OGIB compared to 34% when CE is conducted more than 15 days after OGIB (12). Similar findings have been reported by Katsinelos et al. who reported a diagnostic yield of 87.5% in patients with overt bleeding who underwent CE during the first 10 days following a bleeding episode, and a diagnostic yield of 11.1% for overt bleeders undergoing CE more than 10 days after the bleeding episode (31).

In the presence of gastrointestinal bleeding and a negative scope, a repeat scope may be considered, however a low yield from repeat scopes has been reported. Selby et al. reported that in patients with OGIB, lesions on CE were found with the same frequency in patients who had only one preceding endoscopic evaluation as compared to those who had multiple endoscopies (32). This was supported by a study of repeat endoscopies prior to CE in which a probable cause was seen in 4% only (33). The ESGE does not recommend routine performance of second look endoscopy prior to CE.

1.1.2.2 Crohn's disease

The gold standard diagnostic tool in Crohn's disease is a full ileo-colonoscopy with biopsies (34). Chromoendoscopy with methylene blue dye-spray targeted biopsies increases diagnostic yield to 43% compared to random and sequential biopsy methods which attain a diagnostic yield of 34% (34)

However several studies have evaluated the use of CE in Crohn's disease (35-39). In a prospective, blinded randomized controlled trial by Solem et al. which compared CE to traditional diagnostic techniques in patients with known or suspected Crohn's disease, the sensitivity of CE was 83% but the specificity was lower (53%) than that of all other tests (40). Therefore, the proven high diagnostic yield of CE versus other imaging modalities may not directly translate into a higher diagnostic accuracy since lesions detected by CE may also be induced by other aetiologies. It is therefore important to interpret CE findings within an appropriate clinical context. A multi-centre prospective trial by Gal et al. recommends the use of the CE Crohn's disease activity index score which evaluates three parameters of small bowel pathology (inflammation, extent of disease and presence of strictures) to improve the

specificity of CE (41). Capsule endoscopy might be more sensitive compared with enterography or enteroclysis combined with computerized tomography (CT) and magnetic resonance imaging (MRI) in patients without endoscopic or clinical suspicion of stenosis (42).

The use of CE in Crohn's disease is limited in that a definitive diagnosis cannot be made as a biopsy cannot be undertaken; and negative CE only excludes current disease activity and cannot definitively exclude a future diagnosis. Although capsule retention is higher in patients with suspected Crohn's disease, the frequency is low (2). Furthermore, data on the cost effectiveness of CE in Crohn's disease is conflicting (43).

1.1.2.3 Small bowel tumours

The majority of small bowel tumours are detected during the work up of OGIB or iron deficiency anaemia, but represent only 3.5-5% of these patients (21, 30). Studies have reported several groups at higher risk for small bowel tumours including patients with non-Hodgkin's lymphoma, hepatic metastasis of previously undiagnosed primary neuroendocrine tumours and malignant melanoma with positive faecal occult blood test. If there is a suspicion of a small bowel tumour at imaging, then endoscopy should be considered over CE in order to avoid capsule retention and to obtain histology. There exists a risk of false negatives in CE with large small bowel tumours and in submucosal masses with missing mucosal component, like neuroendocrine tumours or gastrointestinal stromal tumours (2). Overall, CE is not recommended in the follow up of treated small bowel tumours because of a lack of data.

1.1.2.4 Inherited polyposis

While endoscopy and colonoscopy examinations remain the definitive diagnostic method in familial adenomatous polyposis, CE has been used in some cases with significant limitations reported (2). Adenomas in the duodenum and peri-ampullary region are poorly defined by CE, as is polyp size estimation. The location of bigger polyps and determination of their exact sizes has shown to be more accurate by MRI than CE (2).

1.1.2.5 Coeliac disease

The current gold standard diagnostic test for coeliac disease is upper endoscopy with duodenal biopsies and small bowel histology demonstrating villous atrophy. In a study of 38 untreated coeliac patients and 38 controls, in whom CE was performed, Murray et al. were unable to show a relationship between either qualitative or quantitative measurements of extent of disease and severity of clinical presentation (44).

The ESGE recommendation is that there is no role for CE to assess the extent of disease or response to a gluten free diet. There may be a role for CE in equivocal cases of coeliac disease or in patients unwilling or unable to undergo conventional endoscopy

1.1.2.6 Miscellaneous

Several gastrointestinal pathologies have not been addressed in the ESGE guidelines. Nevertheless, smaller studies have explored the use of CE in these conditions, namely vascular malformations, diverticular disease, cryptogenic multifocal ulcerous stenosing enteritis and helminth infestations of the gastrointestinal tract.

Vascular malformations of the gastrointestinal tract

Vascular malformations are classified as arteriovenous malformations, haemangiomas, telangiectasia or other disorders of the connective tissue affecting blood vessels (45). Diagnosis of vascular malformations is usually based on endoscopic imaging or angiography.

Endoscopy investigation may identify many lesions, though it may be difficult to localize the exact lesion responsible for recent or chronic bleeding. Small-bowel video-CE can be considered for noninvasive visualization of the entire small bowel. In one multicenter trial involving 30 subjects known with hereditary haemorrhagic telangiectasia (HHT) presenting with severe anaemia, CE detected gastric and small-bowel telangiectasias in 14 (46.7%) and 26 (86.7%) cases, respectively. Active bleeding was present in 36.7% of cases and diffuse telangiectasias in 42.3% without correlation with age, sex, or type of HHT mutation (46).
Capsule endoscopy makes possible precise mapping of lesions and has a considerable impact on the management of selected patients with HHT (46).

Diverticular disease

Colonic diverticulosis refers to mucosal herniation though the colonic wall, resulting in small outpouchings. This condition arises from both increased intra luminal pressure and a weakened bowel wall (47).

Computerised tomography is the safest and most cost-effective diagnostic method for diagnosing diverticular disease and has an additional potential for use in guiding percutaneous aspiration of abscesses (48, 49). There is little role for CE in colonic pathologies and therefore CE has been infrequently utilized in diverticulosis.

Cryptogenic multifocal ulcerous stenosing enteritis

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is a rare condition characterised by chronic or relapsing moderate ileus episodes resulting from multiple small intestinal strictures and multiple shallow ulcers of the small bowel (50). The aetiology of CMUSE has not been clarified yet and pathogenesis is still poorly understood.

Typical colonoscopic features of CMUSE include multiple small intestinal stenosis and shallow ulcers. Histology reveals an inflammatory infiltrate of plasma cells, monocytes, neutrophils and eosinophils. Mesenteric arteriography is required to exclude features of arteritis (51). This condition bears a significant risk of CE retention, and although CE is useful in the diagnosis, device assisted enteroscopy remains the gold standard for diagnosis (52).

Worm infestation and video capsule endoscopy

Helminths, which are endemic in developing countries, are the most widespread infectious agents that affect human populations. It is estimated that over one billion people in the developing countries are infected with one or more species of helminths, which are transmitted through contact with infected faeces (53).

Helminth infestation carries a high morbidity (54). Although there is a lack of data on the frequency of worm infestation as a cause for gastrointestinal bleeding, hookworm infestation has been reported to be an important cause of OGIB in a few case reports and series from endemic areas (55-58) and intestinal helminth disease is sometimes encountered during investigations of anaemia (59). Capsule endoscopy facilitates imaging of parasites in the small intestine and enables evaluation of the success of therapy after the administration of anthelmintics (60).

1.1.3 Impact of capsule endoscopy on management

The exact significance of the lesions identified on CE and their impact on clinical outcome has not consistently been evaluated for all endoscopic modalities. Several studies have demonstrated a change in patient management and improved outcomes following CE (28, 61). However prospective comparative trials have not consistently confirmed these results (27, 62-66). Capsule endoscopy findings have resulted in a change of management in between 32.3-50% of patients (61, 67). Interestingly, Gubler et al. noted that their findings on CE could be predicted clinically in 73% and no further procedures were required in 80% of these patients (68). In only 10% was gastric or colonic pathology found that had not been previously detected on endoscopy or colonoscopy. Capsule endoscopy findings changed clinical management in only 17%. They recommend that repetition of standard endoscopy and colonoscopy may be useful in patients prior to further imaging with CE or other modalities (68).

Many studies conclude that the usefulness of CE is improved when interpreted in combination with other diagnostic strategies to ensure a more accurate diagnosis. Careful review of the entire recording time of CE may result in a lesion detection rate of up to 35-75% (12, 13). Repeat CE should be considered in patients with persistent obscure gastrointestinal bleeding when the initial study is negative or inconclusive. The cost effectiveness of this recommendation and likely yield is yet to be proven. Overall, the cause for bleeding is not found in 28.6% of patients and the treatment of patients having normal CE remains a dilemma (4).

1.1.4 Comparison between capsule endoscopy and other modalities

Push enteroscopy

Small bowel CE is recommended as the next step procedure after a negative upper endoscope (61). Capsule endoscopy has been found to be superior to push enteroscopy, the procedure of using an endoscope for the direct visualization of the small bowel, and small bowel

radiography in the evaluation of small bowel diseases, including tumours and Crohn's disease (5, 8, 9, 16). Many studies have reported a higher diagnostic rate with push enteroscopy (40-83%) than with other diagnostic methods in the setting of obscure gastrointestinal bleeding (5).

Push enteroscopy is useful in locating a cause for small intestinal bleeding and reported yields vary from 13 - 38.7% (39). However, CE has been shown to be significantly superior to push enteroscopy in identifying intestinal bleeding sites (69).

Small bowel barium radiography

In a meta-analysis comparing CE versus small bowel barium radiography, the yield of clinically significant findings was 42% in CE versus 6% in small bowel barium radiography (70). Capsule endoscopy has also been shown to compare favourably with small bowel cross-sectional imaging for the detection of mucosal lesions consistent with Crohn's disease (71).

Device assisted enteroscopy

Device assisted enteroscopy such as single- and double-balloon enteroscopy (DBE) has largely replaced push enteroscopy (72). Double-balloon enteroscopy is also known as push-and-pull enteroscopy and is a newer diagnostic method that allows complete visualization, biopsy, and treatment of lesions in the small bowel. The overall diagnostic yield of device assisted enteroscopy was 80%, which was 20% higher than the yield reported from CE in a German study (73). Spiral enteroscopy, a procedure involving the pleating of small bowel onto an overtube, is two operator dependent and has a shorter examination time in comparison to DBE (74). In one prospective study, spiral enteroscopy was inferior to CE, detecting only 53.6% of findings on CE (75). Preliminary data on a mechanized version of spiral enteroscopy, called power spiral, is yet to be peer reviewed.

Computed tomography and magnetic resonance Imaging

Capsule endoscopy is also superior to CT angiography in determining the cause of bleeding in patients with OGIB and a significantly higher overall diagnostic yield from immediate CE compared to CT has been reported (27). Capsule endoscopy has been shown to improve the detection of lesions in the proximal small bowel when compared to both CT and MRI (76).

1.1.5 Complications of capsule endoscopy

Capsule retention, defined as the presence of capsule in the digestive tract for more than two weeks, is reported to occur in 0.75 to 5% of cases (9). In a large retrospective study of 2300 patients including 301 known with Crohn's disease, of whom 196 had definitive small bowel involvement, Viazis et al. reported capsule retention in five patients (1.66%), two of whom eventually required surgical removal (77). Most entrapment occurs in the small intestine usually at the site of the small bowel pathology. Risk factors for entrapment include the use of non-steroidal anti-inflammatory drugs, prior abdominal radiation, Crohn's disease, and prior major abdominal surgery.

To minimize the risk of entrapment, patency capsule, a self-dissolving dummy capsule with the same size as the CE, can be administered and high-risk patients can have barium small bowel series instead of CE. Cases of capsule retention can often be managed conservatively with anti-inflammatory agents or immunomodulators. If the capsule fails to pass spontaneously, then retrieval by endoscopy should be attempted. Only a minority of patients require surgery to retrieve a retained capsule (2).

Capsule aspiration

This rare complication has been described in 12 published case reports and in a review of a large number of endoscopic studies (78). Lucendo et al. described this infrequent complication in their study of 136 capsule endoscopes. Risk factors for capsule aspiration include advanced age, poor dentition and central nervous system depressants (78).

None of the documented cases reported had a fatal outcome. It is recommended that patients who are known with swallowing difficulties or who experience difficulties swallowing the capsule have the capsule administered by a delivery device. If the capsule is suspected to have been aspirated into the airways and the patient cannot dislodge it by coughing repeatedly, the most efficient method is to remove it by rigid or flexible bronchoscopy (78).

1.1.6 Capsule Endoscopy: South African literature

There is a paucity of data regarding endoscopy in South Africa. Watermeyer et al undertook a survey to better determine the GI services provided in the Western Caper in 2008. They concluded that owing to the lack of adequate equipment, inadequate scope maintenance and disinfection and a shortage of trained staff, the endoscopic services of the Western Cape were suboptimal (79).

In KZN, a postal survey to 12 department heads was undertaken to determine the availability and adequacy of GI services in the publicly funded healthcare system as compared to internationally recommended standards.(80). The study found that there was poor infrastructure and equipment, frequent service disruptions, resulting in exceedingly long waiting times and insufficient endoscopic training (80). This study highlighted that there is one centre in KwaZulu-Natal that provides capsule endoscopy service for the estimated 8.5 million people accessing health care via the publicly funded healthcare system.

1.1.7 Rationale for this study

However, capsule endoscopy has been introduced in several centres, both in the public and private sectors. In a single report of combined cohort from the public and private sector from Western Cape, CE was performed for occult bleeding in 66% and overt bleeding (34%). The overall yield from capsule endoscopy was 54.1%, and angioectasia was the commonest abnormality (81).
Capsule endoscopy was introduced at IALCH in KZN in 2013, and this is the first report of our experience.

1.2 References

1. Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World Journal of Gastroenterology. 2013;19(24):3726.
2. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2015;47(4):352-76.
3. Swain P. Wireless capsule endoscopy. GUT. 2003;52(suppl 4):iv48-iv50.
4. Singeap A-M, Stanciu C, Trifan A. Capsule endoscopy: the road ahead. World Journal of Gastroenterology. 2016;22(1):369.
5. Liu M-K, Yu F-J, Wu J-Y, et al. Application of capsule endoscopy in small intestine diseases: analysis of 28 cases in Kaohsiung Medical University Hospital. The Kaohsiung Journal of Medical Sciences. 2006;22(9):425-31.
6. Saito Y, Saito S, Oka S, et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointestinal Endoscopy. 2015;82(5):861-9.
7. Pilz JB, Portmann S, Peter S, Beglinger C, Degen L. Colon capsule endoscopy compared to conventional colonoscopy under routine screening conditions. BMC Gastroenterology. 2010;10(1):66.
8. Eliakim R, Yassin K, Niv Y, Metzger Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy. 2009;41(12):1026-31.
9. Qureshi S, Ghazanfar S, Dawood A, et al. An experience of capsule endoscopy from a tertiary care hospital in Pakistan. JPMA-Journal of the Pakistan Medical Association. 2010;60(12):1001.
10. Lai LH, Wong GL, Chow DK, et al. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. The American Journal of Gastroenterology. 2006;101(6):1224.
11. Tang S-j, Haber GB. Capsule endoscopy in obscure gastrointestinal bleeding. Gastrointestinal Endoscopy Clinics. 2004;14(1):87-100.
12. van Turenhout ST, Jacobs MA, van Weyenberg SJ, et al. Diagnostic yield of capsule endoscopy in a tertiary hospital in patients with obscure gastrointestinal bleeding. Journal of Gastrointestinal & Liver Diseases. 2010;19(2).
13. Delvaux M, Friedman S, Keuchel M, et al. Structured terminology for capsule endoscopy: results of retrospective testing and validation in 766 small-bowel investigations. Endoscopy. 2005;37(10):945-50.
14. Levin DA, Watermeyer GA, Deetlefs E, Metz DC, Thomson SR. The efficacy of endoscopic therapy in bleeding peptic ulcer patients. South African Medical Journal. 2012;102(5):290-3.
15. Klein A, Gralnek IM. Video capsule endoscopy for triage of patients with acute upper GI hemorrhage: Is seeing believing? Gastrointestinal Endoscopy. 2016;84(6):914-6.
16. Valenzuela JE, Zaragoza GC, Jorquera EI, et al. Historical analysis of experience with small bowel capsule endoscopy in a Spanish tertiary hospital. Gastroenterología y Hepatología (English Edition). 2017;40(2):70-9.
17. Raju GS, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. Gastroenterology. 2007;133(5):1694-6.
18. Fisher L, Krinsky ML, Anderson MA, et al. The role of endoscopy in the management of obscure GI bleeding. Gastrointestinal Endoscopy. 2010;72(3):471-9.

19. Teshima CW, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. Journal of Gastroenterology and Hepatology. 2011;26(5):796-801.
20. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. GUT. 2011;60(10):1309-16.
21. Koulaouzidis A, Rondonotti E, Giannakou A, Plevris JN. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. Gastrointestinal Endoscopy. 2012;76(5):983-92.
22. Rubin M, Hussain SA, Shalomov A, et al. Live view video capsule endoscopy enables risk stratification of patients with acute upper GI bleeding in the emergency room: a pilot study. Digestive Diseases and Sciences. 2011;56(3):786-91.
23. Gralnek I, Ching J, Maza I, et al. Capsule endoscopy in acute upper gastrointestinal hemorrhage: a prospective cohort study. Endoscopy. 2013;45(01):12-9.
24. Sung JJ, Tang RS, Ching JY, Rainer TH, Lau JY. Use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. Gastrointestinal Endoscopy. 2016;84(6):907-13.
25. Almeida N, Figueiredo P, Lopes S, et al. Urgent capsule endoscopy is useful in severe obscure- overt gastrointestinal bleeding. Digestive Endoscopy. 2009;21(2):87-92.
26. Lecleire S, Iwanicki-Caron I, Di-Fiore A, et al. Yield and impact of emergency capsule enteroscopy in severe obscure-overt gastrointestinal bleeding. Endoscopy. 2012;44(4):337.
27. Leung WK, Ho SS, Suen B-Y, Lai LH, Yu S, Ng EK, et al. Capsule endoscopy or angiography in patients with acute overt obscure gastrointestinal bleeding: a prospective randomized study with long-term follow-up. The American Journal of Gastroenterology. 2012;107(9):1370.
28. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. The American Journal of Emergency Medicine. 2014;32(8):823-32.
29. Mergener K, Ponchon T, Gralnek I, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Endoscopy. 2007;39(10):895-909.
30. Rondonotti E, Marmo R, Petracchini M, de Franchis R, Pennazio M. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. Digestive and Liver Disease. 2013;45(3):179-85.
31. Katsinelos P, Chatzimavroudis G, Terzoudis S, Patsis I, Fasoulas K, Katsinelos T, et al. Diagnostic yield and clinical impact of capsule endoscopy in obscure gastrointestinal bleeding during routine clinical practice: a single-center experience. Medical Principles and Practice. 2011;20(1):60-5.
32. Selby W. Can clinical features predict the likelihood of finding abnormalities when using capsule endoscopy in patients with GI bleeding of obscure origin? Gastrointestinal Endoscopy. 2004;59(7):782-7.
33. Gilbert D, O'malley S, Selby W. Are repeat upper gastrointestinal endoscopy and colonoscopy necessary within six months of capsule endoscopy in patients with obscure gastrointestinal bleeding? Journal of Gastroenterology and Hepatology. 2008;23(12):1806-9.
34. Marion JF, Waye JD, Present DH, et al. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory

bowel disease patients: a prospective endoscopic trial. The American Journal of Gastroenterology. 2008;103(9):2342.
35. Dionisio PM, Gurudu SR, Leighton JA, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. The American Journal of Gastroenterology. 2010;105(6):1240.
36. Kalla R, McAlindon ME, Drew K, Sidhu R. Clinical utility of capsule endoscopy in patients with Crohn's disease and inflammatory bowel disease unclassified. European Journal of Gastroenterology & Hepatology. 2013;25(6):706-13.
37. Mehdizadeh S, Chen G, Enayati P, et al. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). Endoscopy. 2008;40(01):30-5.
38. Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC. The utility of capsule endoscopy in patients with suspected Crohn's disease. The American Journal of Gastroenterology. 2009;104(11):2734.
39. Lewis B, Eisen G, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy. 2007;39(04):303-8.
40. Solem CA, Loftus EV, Fletcher JG, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointestinal Endoscopy. 2008;68(2):255-66.
41. Gal E, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Digestive Diseases and Sciences. 2008;53(7):1933-7.
42. Jensen MD, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. Clinical Gastroenterology and Hepatology. 2011;9(2):124-9. e1.
43. Rondonotti E, Soncini M, Girelli C, et al. Cost estimation of small bowel capsule endoscopy based on "real world" data: Inpatient or outpatient procedure? Digestive and Liver Disease. 2010;42(11):798-802.
44. Murray JA, Rubio–tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clinical Gastroenterology and Hepatology. 2008;6(2):186-93.
45. Gordon FH, Watkinson A, Hodgson H. Vascular malformations of the gastrointestinal tract. Best Practice & Research Clinical Gastroenterology. 2001;15(1):41-58.
46. Grève E, Moussata D, Gaudin JL, et al. High diagnostic and clinical impact of small-bowel capsule endoscopy in patients with hereditary hemorrhagic telangiectasia with overt digestive bleeding and/or severe anemia. Gastrointestinal Endoscopy. 2010;71(4):760-7.
47. Ferzoco L, Raptopoulos V, Silen W. Acute diverticulitis. New England Journal of Medicine. 1998;338(21):1521-6.
48. McKee R, Deignan R, Krukowski Z. Radiological investigation in acute diverticulitis. British Journal of Surgery. 1993;80(5):560-5.
49. Neff C, Vansonnenberg E, Casola G, et al. Diverticular abscesses: percutaneous drainage. Radiology. 1987;163(1):15-8.
50. Birkedal-Hansen H, Moore W, Bodden M, et al. Matrix metalloproteinases: a review. Critical Reviews in Oral Biology & Medicine. 1993;4(2):197-250.
51. Chang DK, Kim JJ, Choi H, et al. Double balloon endoscopy in small intestinal Crohn's disease and other inflammatory diseases such as cryptogenic multifocal ulcerous stenosing enteritis (CMUSE). Gastrointestinal Endoscopy. 2007;66(3):S96-S8.

52. Tachecí I, Ryška A, Rejchrt S, et al. Spontaneous disintegration of a retained video capsule in a patient with cryptogenic multifocal ulcerous stenosing enteritis: a rare complication. Endoscopy. 2008;40(S 02):E104-E5.
53. Hotez PJ, Brindley PJ, Bethony JM, et al. Helminth infections: the great neglected tropical diseases. The Journal of Clinical Investigation. 2008;118(4):1311-21.
54. World Health Organization. Research priorities for helminth infections: technical report of the TDR disease reference group on helminth infections: World Health Organization; 2012. available online at https://apps.who.int/iris/handle/10665/75922
55. Ghoshal UC, Lakshmi CP, Kumar S, et al. Capsule endoscopy for obscure gastrointestinal bleeding in the tropics: report from India. Digestive Endoscopy. 2011;23(1):17-23.
56. Sharma BC, Bhasin DK, Makharia G, et al. Diagnostic value of push-type enteroscopy: a report from India. The American Journal of Gastroenterology. 2000;95(1):137.
57. Das K, Sarkar R, Dasgupta J, et al. Obscure GI bleeding in the tropics: impact of introduction of double-balloon and capsule endoscopies on outcome. Gastrointestinal Endoscopy. 2010;72(2):292-300.
58. Sriram P, Rao G, Reddy DN. Wireless capsule endoscopy: experience in a tropical country. Journal of Gastroenterology and Hepatology. 2004;19(1):63-7.
59. Ghoshal UC, Venkitaramanan A, Verma A, Misra A, Saraswat VA. Hookworm infestation is not an uncommon cause of obscure occult and overt gastrointestinal bleeding in an endemic area: A study using capsule endoscopy. Indian Journal of Gastroenterology. 2015;34(6):463-7.
60. Hosoe N, Imaeda H, Okamoto S, et al. A case of beef tapeworm (Taenia saginata) infection observed by using video capsule endoscopy and radiography (with videos). Gastrointestinal Endoscopy. 2011;74(3):690-1.
61. Albert JG, Schülbe R, Hahn L, et al. Impact of capsule endoscopy on outcome in mid-intestinal bleeding: a multicentre cohort study in 285 patients. European Journal of Gastroenterology & Hepatology. 2008;20(10):971-7.
62. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology. 2004;126(3):643-53.
63. Carey EJ, Leighton JA, Heigh RI, et al. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. The American Journal of Gastroenterology. 2007;102(1):89.
64. Sidhu R, Sanders DS, Kapur K, Leeds JS, McAlindon ME. Factors predicting the diagnostic yield and intervention in obscure gastrointestinal bleeding investigated using capsule endoscopy. Journal of Gastrointestinal and Liver Disease. 2009;18(3):273-8.
65. De Leusse A, Vahedi K, Edery J, et al. Capsule endoscopy or push enteroscopy for first-line exploration of obscure gastrointestinal bleeding? Gastroenterology. 2007;132(3):855-62.
66. Laine L, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial versus dedicated small bowel radiography. Gastroenterology. 2010;138(5):1673-80. e1.
67. Neu B, Ell C, May A, Schmid E, et al. Capsule endoscopy versus standard tests in influencing management of obscure digestive bleeding: results from a German multicenter trial. The American Journal of Gastroenterology. 2005;100(8):1736.

68. Gubler C, Fox M, Hengstler P, et al. Capsule endoscopy: impact on clinical decision making in patients with suspected small bowel bleeding. Endoscopy. 2007;39(12):1031-6.
69. Mylonaki M, Fritscher-Ravens A, Swain P. Wireless capsule endoscopy: a comparison with push enteroscopy in patients with gastroscopy and colonoscopy negative gastrointestinal bleeding. GUT. 2003;52(8):1122-6.
70. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. The American Journal of Gastroenterology. 2005;100(11):2407.
71. Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. Gastrointestinal Endoscopy. 2011;74(1):167-75.
72. Gerson LB. Double-balloon enteroscopy: the new gold standard for small-bowel imaging? Gastrointestinal Endoscopy. 2005;62(1):71-5.
73. May A, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. Gastrointestinal Endoscopy. 2005;62(1):62-70.
74. Baniya R, Upadhaya S, Subedi SC, Khan J, Sharma P, Mohammed TS, et al. Balloon enteroscopy versus spiral enteroscopy for small-bowel disorders: a systematic review and meta-analysis. Gastrointestinal endoscopy. 2017;86(6):997-1005.
75. Buscaglia JM, Richards R, Wilkinson MN, Judah JR, Lam Y, Nagula S, et al. Diagnostic Yield of Spiral Enteroscopy When Performed for the Evaluation of Abnormal Capsule Endoscopy Findings. Journal of Clinical Gastroenterology. 2011;45(4):342-6.
76. Fork F-T, Karlsson N, Kadhem S, Ohlsson B. Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with failed and uncertain passage of a patency capsule. BMC Medical Imaging. 2012;12(1):3.
77. Viazis N, Zacharakis G, Saprikis E, et al. A single center experience of 2300 consecutive patients undergoing capsule endoscopy: indications and diagnostic yield. Endoscopy. 2011;43:A129.
78. Lucendo AJ, González-Castillo S, Fernández-Fuente M, De Rezende LC. Tracheal aspiration of a capsule endoscope: a new case report and literature compilation of an increasingly reported complication. Digestive Diseases and Sciences. 2011;56(9):2758.
79. Watermeyer G, Van Wyk M, Goldberg P. An audit of provincial gastroenterology services in the Western Cape. South African Journal of Surgery. 2008;46(3):68-72.
80. Loots E, Clarke D, Newton K, Mulder C. Endoscopy services in KwaZulu-Natal Province, South Africa, are insufficient for the burden of disease: Is patient care compromised? South African Medical Journal. 2017;107(11):1022-5.
81. Machiridza TR, Deetlefs E, Setshedi M, Thomson S. Small-bowel capsule endoscopy: Experiences from the Western Cape, South Africa. South African Medical Journal. 2019;109(8):611.

Chapter 2: A submission ready manuscript

Capsular Endoscopy: A Single Centre Experience

Naicker N[1], Newton KA[2], Cassim B[3]
[1]Division of Medicine and [2]Departments of Gastroenterology and [3]Geriatrics. School of Clinical Medicine, University of KwaZulu-Natal. Durban. South Africa

Abstract

Background: Capsule endoscopy (CE) is a relatively new modality in the assessment of obscure occult and obscure overt gastroenterological (GI) bleeding in South Africa.

Objectives: The aim of this study was to describe the indications, findings and outcomes of CE at a referral hospital in the public sector in Kwa-Zulu Natal (KZN).

Methods: Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of Kwa-Zulu Natal (UKZN). A retrospective electronic chart review of 27 subjects who underwent CE from its introduction in 2013 to 2018 was undertaken. A structured data sheet was used to extract demographic and clinical details and the endoscopist's report.

Indications were classified as obscure occult GI bleeding, obscure overt GI bleeding, suspected Crohn's disease and unexplained macrocytic anaemia (in a single subject).

The findings at endoscopy were categorised as vascular (angiodysplasia, varices), inflammatory (villous oedema, erythematous mucosa erosions, ulcers or stenosis), normal, inconclusive or other (villous atrophy, polyps, tumours).

Results: The mean age of the 27 patients was 51.2 years ± 21.3 years, with a majority of women (15; 56%) and 12 (44.4%) men. The most common indications for CE were either obscure occult GI bleeding or obscure overt GI bleeding. One patient each had unexplained anaemia and suspected Crohn's disease. All subjects had had previous oesophagogastroduodenoscopy (OGD) and colonoscopy prior to the CE, 15 subjects (55.5%) had had a CT scan of the abdomen and seven (26%) underwent red cell scans.

Of the 14 subjects with occult GI bleeding, 12 had severe iron deficiency anaemia, with symptom duration ranging from one year to 40 years. These subjects had undergone a minimum of one up to a maximum of six OGDs, with a total of 38 OGDs prior to CE. Abnormal findings on CE were reported in nine subjects (64.3%), the commonest of which was inflammatory, and a definitive diagnosis was made in six (42.9%) subjects.

The 11 subjects with obscure overt GI bleeding had undergone a total of 27 prior OGDs prior to CE. Abnormal findings on CE were reported in three of the 11 subjects (27.3%) with obscure overt GI bleeding and a definitive diagnosis made in two subjects (18%).

In addition, the diagnosis was supported in the patient with Crohn's disease, who had been symptomatic for eight years and had had several previous OGDs and colonoscopies.

In the total group who underwent CE, nine (33.3%) subjects had attained a definitive diagnosis. A further 18.5% attained a diagnosis following subsequent investigations. In three subjects (11.1%) the initial indication resolved requiring no further therapy or investigation and two patients (7.4%) were lost to follow up.

Capsule retention occurred in two patients and the capsule was successfully retrieved via laparoscopic surgery.

Conclusion: Capsule endoscopy is a useful modality to further investigate select patients with unexplained GI bleeding, including the identification of lesions outside the small bowel. A guideline for the application of CE in the South African context is required.

Introduction

Gastrointestinal (GI) bleeding is a common condition and in the majority of patients the site of bleeding is identified by traditional, luminal endoscopies. In a smaller proportion, bleeding may be obscure, which is defined as persistent or recurrent GI bleeding undetected by oesophagogastroduodenoscopy (OGD) and colonoscopy. This is further divided into obscure overt (visible bleeding from the GI tract) and obscure occult (iron deficiency anaemia or positive faecal occult blood test) GI bleeding.

The small intestine is long and narrow with unrestricted motility and therefore confounds traditional diagnostic techniques. Capsule endoscopy (CE) was first introduced in 2001 to improve the imaging of the GI tract and assist in the diagnosis of small intestinal pathology.[1]

Capsule endoscopy, a wireless, ingestible capsule, captures images of the GI tract mucosa while being propelled by peristalsis (Figures 1 and 2). Images are transmitted to a data recorder carried by the patient and later uploaded and compiled into a video. Its main advantages are that it is non-invasive, well tolerated, and a relatively safe examination of the small bowel with a diagnostic yield superior to radiological investigation.[2]

Figure 1: PillCam™ Ingestible capsule

Figure 2 a: Normal small bowel

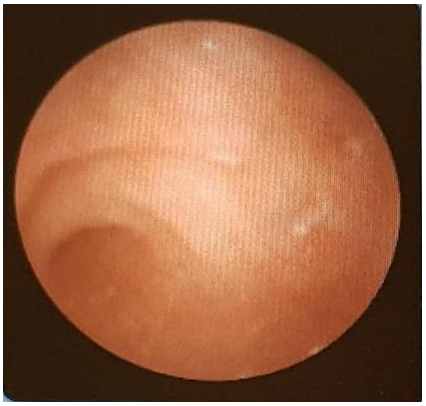

Figure 2b Normal colon

Images obtained from the manufacturer's database

The European Society of Gastrointestinal Endoscopy (ESGE) Clinical guideline recommends the use of CE in patients with obscure GI bleeding (OGIB), Crohn's disease, coeliac disease and small bowel tumours.[3]

Capsule endoscopy has high diagnostic usefulness and is superior to most traditional diagnostic techniques in the detection of small bowel pathology, with an increased detection rate and a sensitivity of 95% and a specificity of 75%.[2] Detection rates vary by indication for CE, the most common being obscure occult GI bleeding. The diagnostic yield varies from 32% to 76%, with an increase in the diagnostic yield of 20 to 40% compared to push enteroscopy and 20% compared to double balloon enteroscopy.[4]

In a systematic review of 172 studies (121 prospective and 51 retrospective) in which 12,369 procedures were undertaken for OGIB, the pooled detection rate was 59.4% ($p < .0001$; 95% CI, 56.5%-62.2%).[5] The detection rates in prospective studies and retrospective studies were 58.8% ($p < .0001$; 95% CI, 55.4%-62.2%) and 60.5% ($p < .0001$; 95% CI, 55.5%-65.5%), respectively.[5] In a further retrospective study of 592 CE procedures, performed for OGIB, a diagnostic yield of 49% was reported.[6] Although Lui et al. determined a lesion detection rate of 85.7% for OGIB, the diagnostic rate was only 35.7%.[2] This variability is due to difficulty in establishing the exact source of bleeding when the bleeding stops prior to or during the procedure. In patients with on-going overt bleeding the yield is higher (87-92%) than with previous overt bleeding or iron deficiency anaemia.[7]

Capsule endoscopy has also been used in Crohn's disease to localise and define the extent of activity of Crohn's disease. In Crohn's disease, while CE had a high sensitivity of 83%, its specificity was lower (53%) than that of all other tests.[8] A CE Crohn's disease activity index score which evaluates three parameters of small bowel pathology (inflammation, extent of disease and presence of strictures) has been proposed to improve the specificity of CE. [9]

Although CE has a good safety profile, capsule retention and rarely capsule aspiration has been described.[7, 10, 11]

In a retrospective review of CE in the Western Cape's public and private health sectors, presented at the 2019 South African Gastroenterology Society Congress, CE was performed for occult bleeding in 66% and overt bleeding in 34%. The overall diagnostic yield was 54.1% and angiodysplasia the commonest finding. [12]

While CE is performed at several centres in South Africa (SA), there are no further reports on the indications, or outcomes. This study was therefore undertaken to document the experience with CE at an academic gastrointestinal unit in KwaZulu-Natal (KZN).

Methodology

Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (UKZN). On site approval was obtained from medical management at Inkosi Albert Luthuli Central Hospital (IALCH) and the provincial Department of Health.

A retrospective electronic chart review, of all subjects who had undergone CE at IALCH, was conducted. This is a quaternary hospital within the public sector of KZN, which receives referrals from district and regional hospitals within the province. The Department provides a 24 hour luminal endoscopic service and is the only centre in KZN with CE services.

All subjects who had undergone CE via Given Imaging *PillCam*^{TM} from initiation of the service (November 2013) to May 2018 were identified from the database stored on the CE modem and included in the study.

The patients' electronic records were retrieved and data on demographics, comorbidities, indications for study, presenting symptoms, number and results prior OGD, colonoscopies, red cell scans and CT scans and findings at CE, were recorded on a structured data sheet. Based on the visual appearance reported by the gastroenterologist, the findings were categorised as vascular (angioectasia, varices), inflammatory (villous oedema, erythematous mucosa erosions, ulcers or stenosis), normal, inconclusive or other (villous atrophy, polyps, tumours) as recommended by the ESGE.[3]

In addition, the haemoglobin and iron study results obtained at the time of CE were extracted from the patients' records. Normal ranges as determined by National Health Laboratory Services at the time of the results were used to determine 'normal' or 'elevated' values. The degree of anaemia was classified as mild (11.0 to 11.9g/dl), moderate (8 to 10.9g/dl) or severe (less than 7.9g/dl) in accordance with the WHO recommendations. [13]

Statistical Analysis:

All data were recorded on an Excel data sheet. De-identified data were entered and analysed using IBM SPSS version 25. Descriptive statistics were used to summarize continuous variables. Frequency tables as well as cross tabulations were used to summarize categorical variables.

Results

Demographic data

The demographic data are shown in Table 1. A total of twenty seven patients, who had undergone 30 CEs were included in the study. The majority were women (15; 56%). The mean age of the total group was 51.2 years ± 21.3 years, with a range from 15 to 83 years. The majority were from the African population group (13 subjects), with 12 Indian and two White subjects.

Comorbidities were present in 12 subjects. The commonest of which was hypertension (Table 1).

All the subjects had had OGD and colonoscopy prior to CE. Twenty three (85.2%) of the subjects had had at least two prior OGDs and twenty one (77.7%) of the subjects had had at least two prior colonoscopies. The subjects with obscure occult GI bleeding had undergone a minimum of one up to a maximum of six OGDs, with a total of 38 OGDs prior to CE. The subjects with obscure overt GI bleeding underwent 27 prior OGDs.

Fifteen subjects (55.5%) had had a CT scan of the abdomen and seven (26%) underwent red cell scans. The most common indications for CE were either obscure occult GI bleeding or obscure overt GI bleeding. One patient had unexplained anaemia and the other suspected small bowel Crohn's disease (Table 2).

Three procedures (10%) were unsuccessful either because a suboptimal image, due to either the presence of bubbles and effluent, or battery failure. These subjects were re-assessed and other diagnostic methods were used for further evaluation.

In two patients, the capsule was not spontaneously released with the stools. The indication for CE in both of these cases was obscure occult GI bleeding. The entrapped CE was successfully retrieved via laparoscopic surgery. A benign stricture of the small bowel was the underlying cause of the retention in one patient and in the other, cryptogenic multifocal ulcerative stenosing enteritis.

Table 1: Baseline demographic and clinical characteristics

		Females (n=15)	Males (n=12)	Total (n=27)
Mean age ± SD in years		54.1 ± 19.4	47.6 ± 22.2	51.2 ± 21.3
Age range		15 - 79	16 - 83	15 - 83
Ethnicity	African	7	6	13
	Indian	7	5	12
	White	1	1	2
Comorbidities	Hypertension	6	3	9 (33.3%)
	Diabetes Mellitus	3	3	6 (22%)
	Osteoarthritis/gout	3	2	5 (18.5%)
	COPD/respiratory disease	2	2	4 (14.8%)
	Valvular heart disease	3	1	4 (14.8%)
	Ischaemic heart disease	2	0	2 (7.4%)
	Arrhythmias	0	2	2 (7.4%)
	Hypothyroidism	1	1	2 (7.4%)
	Renal failure	1	1	2 (7.4%)
	Dyslipidaemia	1	1	2 (7.4%)
	Prostatic disease	0	1	1 (3.7%)
	HIV	1	0	1 (3.7%)
Previous investigations				
	Upper endoscopy	15	12	27
	Colonoscopy	15	12	27
	CT scan abdomen	9	6	15
	Red cell scan	4	3	7

COPD: chronic obstructive pulmonary disease; CT: computerised tomography HIV: Human immunodeficiency virus positivity SD: standard deviation

Table 2: Indications for capsule endoscopy

Indication	Number n=27(%)	Men	Women
Obscure occult gastrointestinal bleeding	14 (51.9%)	4	10
Obscure overt gastrointestinal bleeding	11 (40.7%)	7	4
Unexplained macrocytic anaemia	1 (3.7%)	0	1
Crohn's disease	1 (3.7%)	1	0

Findings at Capsule Endoscopy

Of the 14 patients with obscure occult bleeding, 12 had severe iron deficiency. These subjects were symptomatic from their anaemia for a period ranging from one year to 40 years, with total blood transfusion requirements from two to 14 units. The subjects had undergone a minimum of one up to a maximum of six OGDs, with a total of 38 OGDs prior to CE.

Of the patients with obscure occult GI bleeding, the majority (9, 64.3%) had abnormal findings reported on CE. These were categorised as vascular (2 subjects) and inflammatory (5 subjects) and other lesions (2 subjects) (Table 3). A definitive diagnosis was made in six subjects (42.9%). This included haemangioma, villous atrophy, jejunal polyps, intestinal worms (Figure 3), jejunal inflammation and haemorrhoids. One male subject had severe anaemia (haemoglobin 3.6g/dl) and no prior history of per rectal bleeding. In view of normal luminal scopes, CE was done to exclude small bowel disease and a final diagnosis of haemorrhoids was confirmed.

Table 3: Findings at capsule endoscopy

	Obscure occult GI bleeding n=14	Obscure overt GI bleeding n=11	Unexplained anaemia n=1	Crohn's disease n=1
Abnormal finding on CE	9 (64.3%)	3 (27.3%)	0 (0%)	1 (100%)
Type of lesion Vascular	2 (22.2%)	0 (0%)	0 (0%)	0 (0%)
Inflammatory	5 (55.6%)	2 (66.7%)	0 (0%)	1 (100%)
Other	2 (22.2%)	1 (33.3%)	1 (100%)	0 (0%)
Definitive diagnosis	5 (35.7%)	2 (18.2%)	1 (100%)	1(100%)

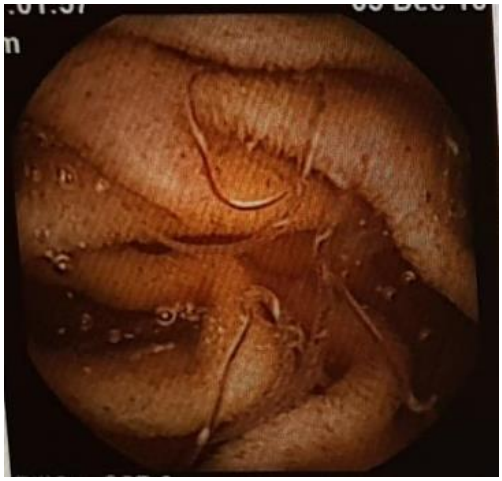

Figure 3: Intestinal worms

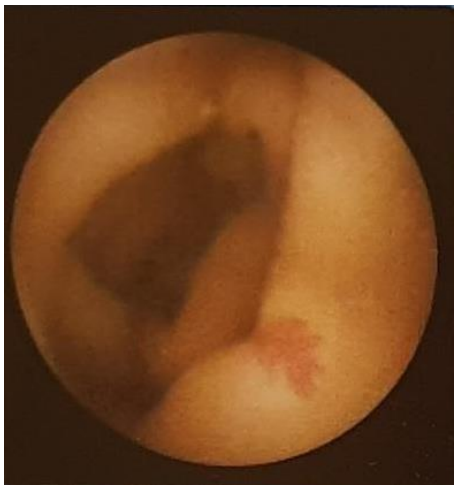

Figure 4: Angiodysplasia

Images from IALCH database

In contrast, abnormal findings on CE were only seen in three of the 11 subjects (27.3%) with obscure overt GI bleeding; two of whom had inflammatory lesions and one a diverticular abscess. A definitive diagnosis was made in two subjects (18%). One subject with antral gastritis experienced resolution following eradication therapy for presumptive helicobacter pylori infection. The other subject, who had no preceding history or suggestive clinical signs of sepsis and a normal prior colonoscopy, had a colonic diverticular abscess diagnosed at CE and recovered following intravenous antibiotic therapy (Table 3).

Crohn's disease

The single subject in this study who underwent CE to further investigate suspected Crohn's disease was a 16 year old male with an 8 year history of diarrhoea. He had had four prior OGDs and three prior colonoscopies with findings suspicious of Crohn's. Histology had not shown villous atrophy or crypt abscess. Prior barium meal showed no strictures. A diagnosis of Crohn's disease was supported by findings at CE of extensive small bowel ulcerations and colitis. The subject responded well to azathioprine, prednisone and mesalazine.

Macrocytic anaemia

A 79 year old female subject underwent CE for the investigation of unexplained, macrocytic anaemia and unintentional weight loss. Her iron studies, serum vitamin b12 and folate were

normal, as were prior OGD and colonoscope. Capsule endoscope showed diffuse gastritis and following eradication therapy, her anaemia resolved.

Discussion

This is the first report of CE in KZN and although this was a small study of 27 subjects, it gives an important glimpse into the utility of CE, albeit in a single quaternary centre.

South Africa has an estimated population of 59 620 000 and a two-tiered health system. The majority of subjects (84%) access the public health sector, whereas approximately 16% use the private health sector. [14] The KZN public sector serves approximately 11 500 000 subjects and CE service is currently provided in one hospital only. In keeping with the demographic profile of patients who access the public health sector, the population groups studied was predominantly African (13 subjects), with 12 Indian and two White subjects.

The wide variance in the age distribution of the subjects is similar to studies from other developing nations like Pakistan and China, where an age range of 15 to 85 years and 31 to 81 years respectively, has been reported. [2,7] This can be attributed to the limited and more recent availability of the CE technology in developing countries. As in our study, all subjects that underwent CE were included in the sample group, whereas in larger trials with stringent exclusion criteria, age profiles are highly selective. Consequently, the mean age of our patients at 51.2 years is younger than other studies. [15-17] In a cost effectiveness analysis the mean age of participants was 65 years, as this was the commonest age at which patients present with upper gastrointestinal bleeding. [18]

The gender distribution in the study is in keeping with some studies, which describe a majority of female subjects ranging from 51% to 57%. [2, 6, 15] Conversely, other studies have shown a significantly greater majority of male subjects, ranging from 53% to 77%. [7, 17, 19] A retrospective review from the Western Cape showed a balanced gender distribution. [12]

Previous procedures

In keeping with the standard recommendation all our subjects had undergone OGD and colonoscopy prior to CE and hence comparable with all other studies.[7] In the total group the mean numbers of OGDs and colonoscopies was 2.29±0.97 and 2.44±1.03, respectively. This compares to that reported by Qureshi et al. who reported a mean 1.61± 0.73 OGDs and 1.25±0.51 colonoscopies.[7] In their study, the OGDs and colonoscopies were normal in 75% and 78%, respectively prior to CE.[7]

Indications

The ESGE recommendation that CE is the first line investigation in patients with OGIB has been widely adopted. [2, 6, 7, 15-18] However most studies do not differentiate between obscure occult GI bleeding and obscure overt GI bleeding.[2, 6, 17, 18] On combining occult and overt GI bleeding in accordance with the American Gastrointestinal Association guidelines, a higher detection rate from CE has been reported.[6] In contrast, several studies have divided their indications into four groups occurring from most to least common, namely occult GI bleeding, overt GI bleeding, inflammatory bowel disease and other, which included polyposis and coeliac disease.[7, 15, 16]

Similar to the studies from Amsterdam, Pakistan and Spain the commonest indication for CE in our study was obscure occult GI bleeding (14 subjects, 56%) followed by obscure overt GI bleeding (11 subjects, 44%). [6, 7, 16] This was congruent with regional findings reported by Machiridza et al. where 66% of studies were to investigate obscure occult GI bleeding and only 34% to investigate obscure overt GI bleeding. [12] In contrast to the majority of studies, in Germany, almost two thirds (62.5%) of the subjects presented with obscure overt GI bleeding.[16]

Findings

A diagnostic yield, the rate at which the procedure detects significant findings, is often used as a proxy estimate of the diagnostic capability of CE.[3] The wide variance in the current diagnostic yield of CE of 38-93% is due to the lack of consensus of the definition of positive findings.[7, 20, 21] In subjects with obscure GI bleeding, a lesion detection rate of 85.7%, but diagnostic yield of 35.7% has been reported.[2] The difference between lesion detection rate and diagnostic yield is because the exact source of bleeding is often difficult to establish when the bleeding stops prior to an examination. In some studies non-specific mucosal changes like red spots, erythema or thickened folds may be considered clinically insignificant, whereas in others, they may be considered to be relevant findings and thus increase the diagnostic yield. [7, 20, 21]

In the majority of studies, vascular lesions commonly angiodysplasia (Figure 4) are the commonest abnormality detected; occurring in 21.4 to 89% of abnormal CE. [2, 6, 12, 15, 16] In our subjects with obscure occult GI bleeding, only two subjects had vascular abnormalities; varices and angioectasia in one patient each. Surprisingly the majority were found to have inflammatory lesions (5; 55.6%). In comparison, Qureshi et al. reported inflammatory lesions, namely ulcerations of the small bowel in 25% of their subjects. [7]

In obscure overt GI bleeding, three subjects had abnormal findings, two of whom were found to have inflammatory lesions. These findings are different to the findings reported by Valenzuela et al. Their retrospective review found vascular lesions in 51%, inflammatory lesions in 13%, normal studies in 8% and inconclusive findings in 3%. [15]

In our study, the diagnostic yield in obscure occult GI bleeding was 42.8%, while the diagnostic yield in obscure overt GI bleeding was lower at 18%. The CE was normal in 63.6% of subjects with overt GI bleeding and 28.6% of subjects with obscure occult GI bleeding. A Chinese study, published in 2006, reviewed the long term follow up of patients with GI bleeding following negative CE and determined that these subjects had low re-bleeding rates, and concluded that in these patients, further invasive investigations can be deferred. [21]

Crohn's disease

Several studies have evaluated the use of CE in Crohn's disease. [22-26] While the ESGE recommends Crohn's disease as an indication, CE has been found to have lower sensitivity compared to other diagnostic modalities and therefore it is important to interpret CE findings within an appropriate clinical context. [8] The single subject in our study who underwent CE to

further investigate suspected Crohn's disease was a 16 year old male with a typical clinical presentation. He had been extensively investigated, and thus visual findings on CE were sufficient to confirm the diagnosis.

In one patient with severe iron deficiency anaemia, a diagnosis of haemorrhoids was made. Despite the fact that CE is primarily intended to detect abnormalities of the small bowel; the capsule is useful in diagnosing abnormalities in other areas too and it is recommended that the entire recording time of VCE be viewed and this may result in additional lesions findings in 35-75% of cases.[4] In our study, 14.8% had CE findings, outside the small bowel, that were determined to be the definitive diagnosis for their GI bleeding.

Capsule retention, defined as the presence of capsule in the digestive tract for more than two weeks, is reported to occur in 0.75 to 5% of cases.[7] Capsule retention is commonly managed expectantly, however in a minority of cases, surgery may be required.[3] Capsule retention occurred in two subjects (7.4%) and both were managed surgically.

Overall outcomes

In summary, 33.3% of patients who underwent CE in this study attained a definitive diagnosis and a further 18.5% attained a diagnosis following subsequent investigations and in three subjects (11.1%) the initial indication resolved requiring no further therapy or investigation and two patients (7.4%) were lost to follow up. In contrast, Albert et al. reported a lack of bleeding source in 23.2% of their subjects with gastrointestinal bleeding. However, of those subjects in whom a bleeding source was identified, 79.9% had definitive diagnosis made. A further 20.1% required on-going investigations. [16]

Capsule images may be obscured by various artefacts and delayed bowel movement can delay capsule transit time. In three subjects the studies were inconclusive (11.1%), likely due to all these factors.

Limitations

This study has several limitations. As an initial report, the study number is small. Furthermore, this is a retrospective chart review and full data was not available in all patients. We did not follow up the patients to determine final outcomes.

Conclusions

Capsule endoscopy is a useful modality to further investigate select patients with unexplained GI bleeding, including the identification of lesions outside the small bowel. A guideline for the application of CE in the South African context is required, given our patient and disease profiles.

References

1. Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World Journal of Gastroenterology. 2013;19(24):3726.
2. Liu M-K, Yu F-J, Wu J-Y, et al. Application of capsule endoscopy in small intestine diseases: analysis of 28 cases in Kaohsiung Medical University Hospital. The Kaohsiung Journal of Medical Sciences. 2006;22(9):425-31.
3. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2015;47(4):352-76.
4. Concha R, Amaro R, Barkin JS. Obscure gastrointestinal bleeding: diagnostic and therapeutic approach. Journal of Clinical Gastroenterology. 2007;41(3):242-51.
5. Liao Z, Gao R, Xu C, Li Z-S. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointestinal Endoscopy. 2010;71(2):280-6.
6. van Turenhout ST, Jacobs MA, van Weyenberg SJ. Diagnostic yield of capsule endoscopy in a tertiary hospital in patients with obscure gastrointestinal bleeding. Journal of Gastrointestinal & Liver Diseases. 2010;19(2).
7. Qureshi S, Ghazanfar S, Dawood A, et al. An experience of capsule endoscopy from a tertiary care hospital in Pakistan. Journal of the Pakistan Medical Association. 2010;60(12):1001.
8. Solem CA, Loftus EV, Fletcher JG, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointestinal Endoscopy. 2008;68(2):255-66.
9. Gal E, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Digestive Diseases and Sciences. 2008;53(7):1933-7.
10. Lucendo AJ, González-Castillo S, Fernández-Fuente M, De Rezende LC. Tracheal aspiration of a capsule endoscope: a new case report and literature compilation of an increasingly reported complication. Digestive Diseases and Sciences. 2011;56(9):2758.
11. Viazis N, Zacharakis G, Saprikis E, et al. A single center experience of 2300 consecutive patients undergoing capsule endoscopy: indications and diagnostic yield. Endoscopy. 2011;43:A129.
12. Machiridza TR, Deetlefs E, Setshedi M, Thomson S. Small-bowel capsule endoscopy: Experiences from the Western Cape, South Africa. South African Medical Journal. 2019;109(8):611.
13. World Health Organization. (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization. https://apps.who.int/iris/handle/10665/85839
14. Naidoo S. The South African national health insurance: A revolution in health-care delivery! Journal of Public Health. 2012;34(1):149-50.
15. Valenzuela JE, Zaragoza GC, Jorquera EI, et al. Historical analysis of experience with small bowel capsule endoscopy in a Spanish tertiary hospital. Gastroenterología y Hepatología (English Edition). 2017;40(2):70-9.
16. Albert JG, Schülbe R, Hahn L, et al. Impact of capsule endoscopy on outcome in mid-intestinal bleeding: a multicentre cohort study in 285 patients. European Journal of Gastroenterology & Hepatology. 2008;20(10):971-7.

17. Sung JJ, Tang RS, Ching JY, Rainer TH, Lau JY. Use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. Gastrointestinal Endoscopy. 2016;84(6):907-13.
18. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. The American Journal of Emergency Medicine. 2014;32(8):823-32.
19. Saito Y, Saito S, Oka S et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointestinal Endoscopy. 2015;82(5):861-9.
20. Tang S-j, Haber GB. Capsule endoscopy in obscure gastrointestinal bleeding. Gastrointestinal Endoscopy Clinics. 2004;14(1):87-100.
21. Lai LH, Wong GL, Chow DK, et al. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. The American Journal of Gastroenterology. 2006;101(6):1224.
22. Dionisio PM, Gurudu SR, Leighton JA, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. The American Journal of Gastroenterology. 2010;105(6):1240.
23. Kalla R, McAlindon ME, Drew K, Sidhu R. Clinical utility of capsule endoscopy in patients with Crohn’s disease and inflammatory bowel disease unclassified. European Journal of Gastroenterology & Hepatology. 2013;25(6):706-13.
24. Mehdizadeh S, Chen G, Enayati P et al. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). Endoscopy. 2008;40(01):30-5.
25. Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC. The utility of capsule endoscopy in patients with suspected Crohn's disease. The American Journal of Gastroenterology. 2009;104(11):2734.
26. Lewis B, Eisen G, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy. 2007;39(04):303-8.

Appendices

Appendix 1: The final Study Protocol

Protocol for MMed

Capsular endoscopy: a single centre experience

Author: Nisholini Naicker

Supervisor: Professor B. Cassim

Co-investigator: Professor KA Newton

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1.1 Summary

Gastrointestinal bleeding is a common condition and in the majority of patients the site of bleeding can be identified by traditional, luminal endoscopies. In a smaller proportion, bleeding may be obscure. These patients may present with iron deficiency anaemia or positive faecal occult blood testing. Endoscopy and colonoscopy may not be helpful particularly in the small bowel. The small bowel is long and narrow, with unrestricted motility, which limits traditional diagnostic techniques.

Capsule endoscopy (CE) was first introduced in 2001 to improve the imaging of the gastrointestinal tract and assist in the diagnosis of small bowel pathology. The European Society of Gastrointestinal Endoscopy (ESGE) Clinical guideline recommends the use of CE in patients with obscure gastrointestinal bleeding, Crohn's disease, Celiac disease and small bowel tumours.

Capsule endoscopy has high diagnostic usefulness and is superior to most traditional diagnostic techniques. Studies have shown an increased detection rate of small bowel pathology by the capsule with a sensitivity of 95% and specificity of 75% (1-3). Although CE has a good safety profile, an important complication of capsule endoscopy is capsule retention.

There have been numerous studies on capsule endoscopy, but only a handful from South Africa. There are no studies from KwaZulu-Natal.

1.2 Aim

To describe the indications, diagnostic yield and safety of capsule endoscopy

1.3 Hypothesis:

Capsule endoscopy is a safe procedure with a high diagnostic yield

1.4 Objectives:

1. To describe the indications for capsule endoscopy in a quaternary referral centre
2. To determine the diagnostic yield for capsule endoscopy in a quaternary referral hospital
3. To determine the safety of capsule endoscopy in a quaternary referral hospital

2.0 Literature review

The small intestine is relatively inaccessible compared to the stomach and large intestine. The length of the small intestine, in addition to its free intra peritoneal location, contractility and overlying loops, confounds traditional diagnostic techniques such as small bowel enema, computerised tomography (CT) scans, push enteroscopy, angiography, and technetium 99m labelled red blood scans.

The small bowel barium series has long been considered the mainstay in the evaluation of the small intestine. Data shows a poor diagnostic yield of 0-5.6% in the investigation of patients with occult bleeding or iron deficiency (4, 5). Consequently, these patients undergo more diagnostic procedures, require more blood transfusions and have a longer hospitalization with higher healthcare expenditure

2.1 Capsule endoscopy

Capsule endoscopy is a wireless, ingestible capsule capable of capturing images of the gastrointestinal tract mucosa while being propelled by peristalsis. These images are transmitted wirelessly to a data recorder carried by the patient and later uploaded to a computer where software compiles them into a video for reading. Capsule endoscopy is also known as mouth to anus (M2A), Video capsule endoscopy (VCE) and Wireless capsule endoscopy (WCE).The exact mechanics of the capsule and the administration and recording process is well described (6).

Several adjustments have been made since its introduction in 2001 including longer battery life, increased image capture frame rate, wider angle of view, and optimization of light control. Additionally, many real time viewing systems are now available which has enabled application in emergency settings. There are several capsule makes available and they largely yield comparable results in terms of diagnostic yield, image quality and completion rate (7).

Capsule endoscopy has had a significant impact in broadening the diagnostic yield of small bowel abnormalities because of its unique ability to assess the small bowel in detail. It is primarily used for the evaluation of obscure gastrointestinal bleeding and has found to be useful in diagnosing several clinical conditions including Crohn's disease, Celiac disease; inflammatory bowel disease, and small bowel tumours. Its main advantages being that it is non-invasive , well tolerated, and a relatively safe examination of the small bowel with a diagnostic yield superior to radiological investigation (8).

A diagnostic yield, the rate in which the procedure detects what are thought to be significant findings, is often used as a proxy estimate of the diagnostic capability of capsule endoscopy (9). The overall lesion detection rate was reported to be as high as 71.4% (8). Several studies have described the specificity of the findings at capsule endoscopy to range from 64-94% (1-3). Current diagnostic yield of capsule endoscopy is reported to be 38-93%; however, the definition of a positive finding is a contested issue (4, 10, 11). In certain studies non-specific mucosal changes like red spots, erythema or thickened folds were considered clinically

insignificant, whereas in others, they may be considered relevant findings and thus increase the diagnostic yield.

Accuracy parameters for capsule endoscopy are not truly known because there is no standard comparative method. Furthermore the indications are heterogeneous and the timing of the capsule endoscopy varies considerably, making it difficult to compare studies. To address this concern, the European Society of Gastrointestinal Endoscopy (ESGE) have introduced structured terminology and guidelines for the clinical application of capsule endoscopy (12, 13).

2.1.1 Indications for Capsule endoscopy

Gastrointestinal bleeding

The most common indication remains the investigation of obscure gastrointestinal bleeding. Other indications include NSAID induced mucosal damage, diagnosis and surveillance of patients with hereditary polyposis syndrome, inflammatory bowel disease, malabsorption syndromes, small bowel tumours, and clarification of small bowel imaging (4). Several studies have defined factors that predict the likelihood of detecting pathology. Specialised indications include acute bleeding, requirement for iron replacement therapy, age over 65, male gender, liver disease and use of NSAIDS or antithrombotic therapy (14).

Bleeding from a peptic ulcer is a common medical emergency and although most upper gastrointestinal bleeding stops spontaneously, 15-20% continue (15). Despite effective endoscopic diagnostic and therapeutic modalities, upper gastrointestinal tract haemorrhage continues to challenge clinicians (16). Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent gastrointestinal bleeding undetected by endoscopy and colonoscopy. This entity is further divided into obscure-overt bleeding, when visible blood is found and obscure occult, which presents with iron deficiency anaemia or positive faecal occult blood testing.

Data on accuracy parameters (sensitivity, specificity, positive predictive value, and negative predictive value and likelihood ratios) of capsule endoscopy in OGIB patient is scarce due to the absence of a gold standard modality and objective criteria for positive findings of CE. Nevertheless, the present evidence on diagnostic usefulness of CE is enough to support the use of CE for OGIB (9, 17, 18).

In a retrospective study of 592 procedures in a tertiary referral hospital in Amsterdam, over a period of 4 years, a diagnostic yield of 49% was reported (12). While Lui et al determined a lesion detection rate of 85.7% for OGIB, the diagnostic rate was only 35.7% (8). The variability in lesion detection and diagnosis is due to the fact that the exact source of bleeding is difficult to establish when bleeding stops prior to or during an examination. In such cases, even though possible lesions may be detected, if multiple lesions are present the main bleeding source is difficult to determine. When the capsule is administered to patients with on-going overt bleeding the yield is higher (87-92%) then with previous overt bleeding or iron deficiency anaemia (4). Overall, however in patients with on-going overt OGIB,

endoscopy should be considered as first line, given its ability to make a diagnosis and to perform therapy at the same time.

In patients with positive capsule endoscopy a subsequent endoscopy is usually performed to confirm and treat lesions. A pooled diagnostic yield of endoscopy performed after previously positive CE was 75.0% and the odds ratio for the yield of endoscopy performed after a previously positive CE, compared with that of endoscopy performed in all patients was 1.79 (9, 19).

Although iron deficiency anaemia is a common indication, it is important that prior to CE a complete medical history (including medication use, co morbidities, and gynaecological history), endoscopy with duodenal and gastric biopsies is undertaken (3). Bidirectional endoscopy identifies the cause of iron deficiency in 70-80% of patients (20). When this is negative, then the small bowel requires further investigation (9, 20). In a systematic review pooling data from four studies based on iron deficiency anaemia, a diagnostic yield of CE was 66% was reported, which is comparable to previous studies (21).

The use of CE in acute gastrointestinal haemorrhage was first reported by Rubin et al who showed that CE could accurately identify high risk and low risk patients and be a useful risk stratification tool to determine the need for therapeutic intervention (22). A modified oesophageal CE, with extended battery life, was demonstrated to be safe and effective in correctly identifying acute gastrointestinal bleeding with a sensitivity of 50%, specificity 66%, positive predictive value of 20% and negative predictive value of 89% in detecting gross gastrointestinal bleeding (23).

Further studies have confirmed the value of CE in the emergency department for patients with acute upper gastrointestinal haemorrhage (23, 24). Furthermore, CE is more accurate than conventional screening tools in correctly predicting high risk and low risk endoscopic stigmata of recent haemorrhage(16). The use of CE as an endoscopic triage tool in patients with suspected acute upper gastrointestinal bleed has also been shown to significantly reduce hospital admission in low risk to moderate risk patients and identify more low risk patients compared to traditional scoring tools(16, 24).

Currently the ESGE recommends emergency CE in patients with ongoing overt OGIB. This is based on two retrospective studies and one randomized control trial comprising of less than 100 patients overall. Emergency CE performed within 24 to 72 hours from admission during severe on-going overt OGIB appears to be an effective modality with a diagnostic yield up to 70% and has a significant impact on patient management (25-27).

In the United states of America (USA), CE is considered cost effective for low and moderate risk patients presenting with acute upper gastrointestinal haemorrhage, compared to the other strategies.as many patients without the need for intervention can be safely discharged home without incurring the costs and potential complications associated with a hospital admission (28).

However, CE may be negative. In 49 patients who underwent CE for OGIB, and in whom CE was negative, a re-bleeding rate of 32.7% was reported (10). Several reviews and consensus recommendations concluded that patients with OGIB and normal CE have a good prognosis with a low risk of re bleeding and should be managed conservatively with no further investigation (29, 30).

Crohn's disease

Colonoscopy is considered the first line investigation for Crohn's disease and is sufficient to establish the diagnosis in the vast majority of patients. However several studies have evaluated the use of CE in Crohn's disease (31-35). A prospective, blinded randomized controlled trial by Solem et al. which compared CE to traditional diagnostic techniques in patients with known or suspected Crohn's disease, the sensitivity of CE 83% but the specificity of CE was lower (53%) than that of all other tests (36). Therefore, the proven high diagnostic yield of CE versus other imaging modalities may not directly translate into a higher diagnostic accuracy since lesions detected by CE may also be induced by other aetiologies. It is therefore important to interpret CE findings within an appropriate clinical context. A multi-centre prospective trial by Gal et al. recommends the use of the CE Crohn's disease activity index score which evaluates three parameters of small bowel pathology (inflammation, extent of disease and presence of strictures) to improve the specificity of CE (37).

The use of CE in Crohn's disease is limited in that a definitive diagnosis cannot be made as a biopsy cannot be undertaken; and negative CE only excludes current disease activity and cannot definitively exclude a future diagnosis. Although capsule retention is higher in patients with suspected Crohn's disease, the frequency is low (9). Furthermore, data on the cost effectiveness of CE in Crohn's disease is conflicting (38).

Familial adenomatous polyps

While endoscopy and colonoscopy examinations remain the definitive diagnostic method in familial adenomatous polyposis, CE has been used in some cases with several limitations reported. Adenomas in the duodenum and periampullary region are poorly defined by CE, as is exact polyp size estimation. Additionally, the location of bigger polyps and determination of their exact sizes has shown to be more accurate by MRI than CE (9).

Coeliac disease

The current gold standard diagnostic test for coeliac disease is endoscopy with duodenal biopsies and small bowel histology demonstrating villous atrophy. In a study of 38 untreated coeliac patients and 38controls, in whom CE was performed, Murray et al. were unable to show a relationship between either qualitative or quantitative measurements of extent of disease and severity of clinical presentation (39).

The ESGE recommendation is that there is no role for CE to assess the extent of disease or response to a gluten free diet. There may be a role for CE in equivocal cases of coeliac disease or in patients unwilling or unable to undergo conventional endoscopy

Small bowel tumours

The majority of small bowel tumours are detected during the work up of OGIB or iron deficiency anaemia, but represent only 3.5-5% of these patients (21, 30). Studies have reported several groups at higher risk for small bowel tumours including patients with non-Hodgkin's lymphoma, hepatic metastasis of previously undiagnosed primary neuroendocrine tumours and malignant melanoma with positive faecal occult blood test. If there is a suspicion of a small bowel tumour at imaging, then endoscopy should be considered over CE in order to avoid capsule retention and to obtain histology. There exists a risk of false negatives in CE with large small bowel tumours and in submucosal masses with missing mucosal component, like neuroendocrine tumours or gastrointestinal stromal tumours (9). Overall, CE is not recommended in the follow up of treated small bowel tumours because of a lack of data.

2.1.3 Impact of Capsule Endoscopy on Management

The exact significance of lesions identified and their impact on clinical outcome has not consistently been evaluated for all endoscopic modalities. Several studies have demonstrated a change in patient management and improved outcomes following CE. However prospective comparative trials have not consistently confirmed these results (27, 40-44). Capsule endoscopy findings have resulted in a change of management between 32.3 -50% (45, 46). Interestingly, Gubler et al noted that their findings on CE could be predicted clinically in 73% and no further procedures were required in 80% of these patients. In only 10% was gastric or colonic pathology found that had not been previously detected on endoscopy or colonoscopy. Capsule endoscopy findings changed clinical management in 17% only. They recommend that repetition of standard endoscopy and colonoscopy may be useful in patients prior to further imaging (47).

Many studies conclude that the usefulness of CE is improved when interpreted in combination with other diagnostic strategies to ensure a more accurate diagnosis. Careful review of the entire recording time of CE may result in a lesion detection rate of up to 35-75% (12). Repeat CE should be considered in patients with persistent obscure gastrointestinal bleeding when the initial study is negative or inconclusive. The cost effectiveness of this recommendation and likely yield is yet to be proven. Overall, the cause for bleeding is not found in 28.6% of patients and the treatment of patients having normal CE remains a dilemma (4).

2.1.4 Timing of Capsule Endoscopy

Several retrospective studies have shown that earlier CE in patients with OGIB is associated with an increased diagnostic yield compared with late CE. Detection rates of up to 92% are seen when CE is performed within 15 days of an OGIB compared to 34% when CE conducted more than 15 days post diagnosis (12). Similar findings have been reported by Katsinelos et al. who reported a diagnostic yield of 87.5% in patients with overt bleeding who underwent CE during the first 10 days following a bleeding episode, and a diagnostic yield of 11.1% for overt bleeders undergoing CE more than 10 days after bleeding episode (48).

In the diagnosis of gastrointestinal bleeding, the presence of a negative scope, a repeat scope may be considered, however a low yield from repeat scopes has been reported. Selby et al. reported that in patients with OGIB, lesions on CE were found with the same frequency in patients who had only one preceding endoscopic evaluation as compared to those who had multiple endoscopies (49). This was supported by a study of repeat endoscopies prior to CE in which a probable cause was seen in 4% only (50). ESGE does not recommend routine performance of second look endoscopy prior to CE.

2.1.5 Comparison between Capsule Endoscopy and other Modalities

Push enteroscopy

Small bowel CE is recommended as the next step procedure after a negative endoscope (46). Capsule endoscopy has been found to be superior to push enteroscopy and small bowel radiography in the evaluation of small bowel diseases, including tumours and Crohn's disease (3, 4, 8, 14). Many studies have reported a higher diagnostic rate (40-83%) than with other diagnostic methods in the setting of obscure gastrointestinal bleeding (8).

In a meta-analysis comparing CE versus small bowel barium radiography for small bowel pathology, the yield of clinically significant findings was 42% in CE versus 6% in small bowel barium radiography (51). Capsule endoscopy has also been shown to compare favourably with small bowel cross sectional imaging for the detection of mucosal lesions consistent with Crohn's disease (52).

Push enteroscopy is useful in locating a cause for small intestinal bleeding and reported yields vary from 13 to 38.7% (35). However, CE has been shown to be significantly superior to push enteroscopy in identifying intestinal bleeding sites (53).

Computed Tomography and Magnetic Resonance Imaging

Capsule endoscopy is also superior to CT angiography in determining the cause of bleeding in patients with OGIB and a significantly higher overall diagnostic yield from immediate CE compared to CT has been reported (27). Capsule endoscopy has been shown to improve the detection of lesions in the proximal small bowel when compared to both CT and magnetic resonance imaging (MRI) (54).

2.1.6 Limitations of Capsule Endoscopy

The major limitations of CE include a lack of therapeutic opportunities and tissue sampling, and uncontrolled propulsion. Capsule endoscopy relies totally on natural bowel peristalsis therefore the capsule progress is non-steerable, and hence more rapid in the proximal than in lower segments of the small-bowel. Presently, several research groups are working to design remotely manoeuvrable capsules capable of recognizing lesions and collecting target tissue samples (7).

Procedure and preparation issues are noted to be significant since certain conditions obscure the images such as gastric bubbles, residual food and blood. Evidence suggests that a preparation regimen based on laxatives is more effective than fasting alone in improving the small bowel mucosa visualization (7). It is recommended that patients with delayed bowel movement and constipation fast for longer and drink more water.

Performing CE in the vicinity of telemetric systems can cause interference in the transmission of images to the recorder, resulting in multiple gaps the videos downloaded. It is therefore recommended to avoid administering the capsule to patients in these vicinities (6).

2.1.7 Complications of Capsule Endoscopy

Capsule retention, defined as the presence of capsule in the digestive tract for more than two weeks, is reported to occur in 0.75 to 5% of cases (4). In a large retrospective study of 2300 patients including 301 known with Crohn's disease, of whom 196 had definitive small bowel involvement, Viazis et al. reported capsule retention in 5 patients (1.66%), 2 of whom eventually required surgical removal (55). Most entrapment occurs in the small intestine usually at the site of small bowel pathology. Risk factors for entrapment include NSAID usage, prior abdominal radiation, Crohn's disease, and prior major abdominal surgery.

To minimize the risk of entrapment, patency capsule, a self-dissolving dummy capsule with the same size as the CE, can be administered and high-risk patients can have barium small bowel series. Cases of capsule retention can often be managed conservatively with anti inflammatory agents or immunomodulators. If the capsule fails to pass spontaneously, then retrieval by endoscopy should be attempted. Only a minority of patients require surgery to retrieve a retained capsule (9).

2.2 Justification of this study

Capsule endoscopy is a relatively new procedure in the evaluation of gastrointestinal disorders, particularly gastrointestinal bleeding, in Inkosi Albert Luthuli Central Hospital (IALCH), a quaternary hospital in KwaZulu-Natal, and has not been previously described. A review of the indications, yield and complications will further refine the role of CE in the assessment of patients with gastrointestinal bleeds at IALCH

3. Study Methods

3.1 Study design

Retrospective review of the electronic records of all patients who have undergone capsule endoscopy at Inkosi Albert Luthuli Central Hospital

3.2 Study setting/location

The gastrointestinal unit at the Inkosi Albert Luthuli Central Hospital. (IALCH)

eThekwini district, Kwa Zulu Natal.

3.3 Study population

All patients who have undergone capsule endoscopy at the IALCH gastrointestinal unit will be enrolled in the study.

1.4 Sampling strategy

Non-probability sampling (convenient sampling) will be employed during the selection process.

Inclusion/Exclusion criteria

All patients that underwent capsule endoscopy will be included in the study. There will no exclusions.

1.6 Data collection methods and tools

Permission will be obtained from data custodian, IALCH hospital manager, to access electronic patient records

Electronic patient records stored on the hospital server will be reviewed by the researcher. All patients having undergone capsule endoscopy in the unit will be reviewed beginning with the most recent and working backwards. The sample will be chosen from all consecutive case files.

Relevant data will be recorded on a standardized data collection tool. This tool will record age, gender, referral diagnosis, co morbid conditions, capsule endoscopy findings, clinical outcome, and adverse events (see appendix).

1.7 Data Management & statistics:

Data collection instruments - Data will be collected by the researcher using a customized data collection instrument (see appendix).

Data entry package: Microsoft Excel 2010 will be used to record raw data.

Data analysis: data will be analysed using descriptive statistics, and the data will be presented in the forms of tables, bar graphs and percentages

Ethical considerations

Ethical approval will be obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal.

Consent will be obtained from the custodian of data, the CEO of the hospital.

This study will be undertaken at no extra cost to the hospital. The data collected is pre-recorded information that is stored on site in an electronic format. Retrieval of the information will be undertaken by the researcher.

The patient's interests will be safe guarded as the patient records will be accessed by a single researcher. Additionally, the researcher will be a medical practitioner, who is bound by conventional professional standards of confidentiality.

The information required will be gender, age, hospital number, referral diagnosis, past medical history.

Patients will not be directly contacted or interviewed. There will be no requirements from Inkosi Albert Luthuli hospital patients or staff.

Following data collection the individuals identifying details will be anonymised –no patient particulars will be given to the statistician

This study procedure and outcome is designed to minimize IALCH hospital risks for adverse outcomes.

The data will be stored for a minimum period of 15 years (until 2033). The data will be stored in a fire resistant cabinet in the Department of Internal Medicine at the University of Kwa Zulu natal.

All electronic copies of data will be stored in external hard drive in the department on a server.

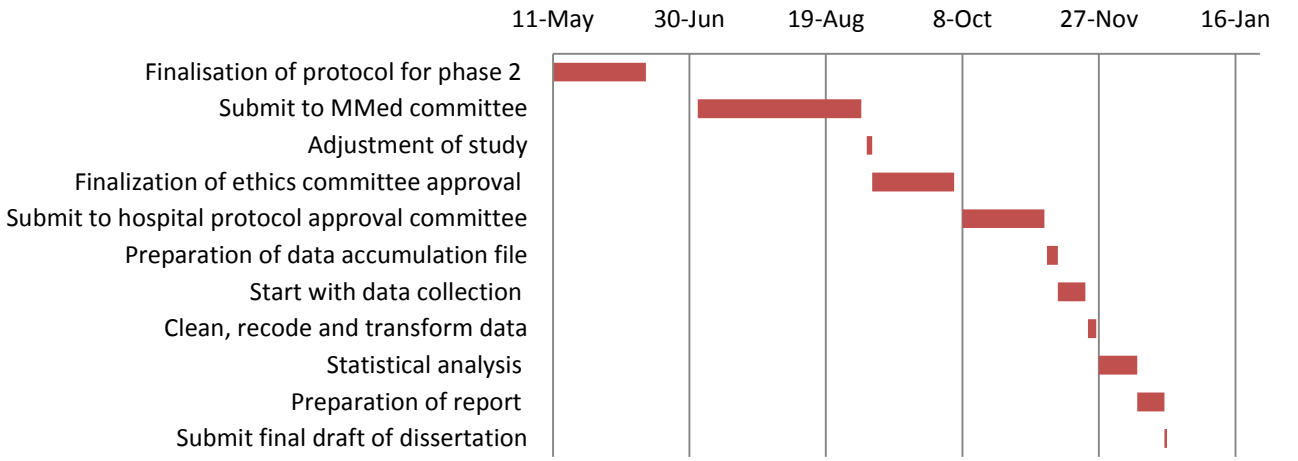
Limitations of the study

The nature of the study, being retrospective and performed in a single centre will limit the acc uracy and power of the study.

The data source will be based on existing records of patient details, it is anticipated that some information may be inappropriately/insufficiently captured

Despite the limitations of a single centre study, the results may be applicable to other institutions in view of the fact that there is a paucity of data in South Africa

Timeline and project management



	Submit final draft of dissertation	Preparation of report	Statistical analysis	Clean, recode and transform data	Start with data collection	Preparation of data accumulation file	Submit to hospital protocol approval committee	Finalization of ethics committee approval	Adjustment of study	Submit to MMed committee	Finalisation of protocol for phase 2
start date	21-Dec	11-Dec	27-Nov	23-Nov	12-Nov	8-Nov	8-Oct	5-Sep	3-Sep	3-Jul	11-May
duration	1	10	14	3	10	4	30	30	2	60	34

References:

1. Saito Y, Saito S, Oka S, Kakugawa Y, Matsumoto M, Aihara H, et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointestinal endoscopy. 2015;82(5):861-9.
2. Pilz JB, Portmann S, Peter S, Beglinger C, Degen L. Colon capsule endoscopy compared to conventional colonoscopy under routine screening conditions. BMC gastroenterology. 2010;10(1):66.
3. Eliakim R, Yassin K, Niv Y, Metzger Y, Lachter J, Gal E, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy. 2009;41(12):1026-31.
4. Qureshi S, Ghazanfar S, Dawood A, Zubair M, Leghari A, Niaz SK, et al. An experience of capsule endoscopy from a tertiary care hospital in Pakistan. JPMA-Journal of the Pakistan Medical Association. 2010;60(12):1001.
5. LewisB G. Reviewarticle: Theadventofcapsuleen□ doscopy—anot□ so□ futuristicapproachtoobscuregastrointestinal bleeding. AlimentPharmacolTher. 2003;17(9):1085r96.
6. Swain P. Wireless capsule endoscopy. Gut. 2003;52(suppl 4):iv48-iv50.
7. Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World journal of gastroenterology: WJG. 2013;19(24):3726.
8. Liu M-K, Yu F-J, Wu J-Y, Wu I-C, Wang J-Y, Hsieh J-S, et al. Application of capsule endoscopy in small intestine diseases: analysis of 28 cases in Kaohsiung Medical University Hospital. The Kaohsiung journal of medical sciences. 2006;22(9):425-31.
9. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2015;47(4):352-76.
10. Lai LH, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. The American journal of gastroenterology. 2006;101(6):1224.
11. Tang S-j, Haber GB. Capsule endoscopy in obscure gastrointestinal bleeding. Gastrointestinal Endoscopy Clinics. 2004;14(1):87-100.
12. van Turenhout ST, Jacobs MA, van Weyenberg SJ, Herdes E, Stam F, Mulder CJ, et al. Diagnostic yield of capsule endoscopy in a tertiary hospital in patients with obscure gastrointestinal bleeding. Journal of Gastrointestinal & Liver Diseases. 2010;19(2).
13. Delvaux M, Friedman S, Keuchel M, Hagenmüller F, Weinstein M, Cave D, et al. Structured terminology for capsule endoscopy: results of retrospective testing and validation in 766 small-bowel investigations. Endoscopy. 2005;37(10):945-50.
14. Valenzuela JE, Zaragoza GC, Jorquera EI, Pujante PT, de las Parras FA, Álvarez FC. Historical analysis of experience with small bowel capsule endoscopy in a Spanish tertiary hospital. Gastroenterología y Hepatología (English Edition). 2017;40(2):70-9.
15. Levin DA, Watermeyer GA, Deetlefs E, Metz DC, Thomson SR. The efficacy of endoscopic therapy in bleeding peptic ulcer patients. SAMJ: South African Medical Journal. 2012;102(5):290-3.
16. Klein A, Gralnek IM. Video capsule endoscopy for triage of patients with acute upper GI hemorrhage: Is seeing believing? Gastrointestinal endoscopy. 2016;84(6):914-6.
17. Raju GS, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. Gastroenterology. 2007;133(5):1694-6.

18. Fisher L, Krinsky ML, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, et al. The role of endoscopy in the management of obscure GI bleeding. Gastrointestinal endoscopy. 2010;72(3):471-9.
19. Teshima CW, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta- analysis. Journal of gastroenterology and hepatology. 2011;26(5):796-801.
20. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. 2011:gut. 2010.228874.
21. Koulaouzidis A, Rondonotti E, Giannakou A, Plevris JN. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. Gastrointestinal endoscopy. 2012;76(5):983-92.
22. Rubin M, Hussain SA, Shalomov A, Cortes RA, Smith MS, Kim SH. Live view video capsule endoscopy enables risk stratification of patients with acute upper GI bleeding in the emergency room: a pilot study. Digestive diseases and sciences. 2011;56(3):786-91.
23. Gralnek I, Ching J, Maza I, Wu J, Rainer T, Israelit S, et al. Capsule endoscopy in acute upper gastrointestinal hemorrhage: a prospective cohort study. Endoscopy. 2013;45(01):12-9.
24. Sung JJ, Tang RS, Ching JY, Rainer TH, Lau JY. Use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. Gastrointestinal endoscopy. 2016;84(6):907-13.
25. Almeida N, Figueiredo P, Lopes S, Freire P, Lérias C, Gouveia H, et al. Urgent Capsule Endoscopy is useful in severe obscure overt gastrointestinal bleeding. Digestive Endoscopy. 2009;21(2):87-92.
26. Lecleire S, Iwanicki-Caron I, Di-Fiore A, Elie C, Alhameedi R, Ramirez S, et al. Yield and impact of emergency capsule enteroscopy in severe obscure-overt gastrointestinal bleeding. Endoscopy. 2012;44(4):337.
27. Leung WK, Ho SS, Suen B-Y, Lai LH, Yu S, Ng EK, et al. Capsule endoscopy or angiography in patients with acute overt obscure gastrointestinal bleeding: a prospective randomized study with long-term follow-up. The American journal of gastroenterology. 2012;107(9):1370.
28. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. The American journal of emergency medicine. 2014;32(8):823-32.
29. Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Endoscopy. 2007;39(10):895-909.
30. Rondonotti E, Marmo R, Petracchini M, de Franchis R, Pennazio M. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. Digestive and Liver Disease. 2013;45(3):179-85.
31. Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. The American journal of gastroenterology. 2010;105(6):1240.
32. Kalla R, McAlindon ME, Drew K, Sidhu R. Clinical utility of capsule endoscopy in patients with Crohn's disease and inflammatory bowel disease unclassified. European journal of gastroenterology & hepatology. 2013;25(6):706-13.
33. Mehdizadeh S, Chen G, Enayati P, Cheng D, Han N, Shaye O, et al. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). Endoscopy. 2008;40(01):30-5.

34. Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC. The utility of capsule endoscopy in patients with suspected Crohn's disease. The American journal of gastroenterology. 2009;104(11):2734.
35. Lewis B, Eisen G, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy. 2007;39(04):303-8.
36. Solem CA, Loftus EV, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointestinal endoscopy. 2008;68(2):255-66.
37. Gal E, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Digestive diseases and sciences. 2008;53(7):1933-7.
38. Rondonotti E, Soncini M, Girelli C, Villa F, Russo A, de Franchis R. Cost estimation of small bowel capsule endoscopy based on "real world" data: Inpatient or outpatient procedure? Digestive and Liver Disease. 2010;42(11):798-802.
39. Murray JA, Rubio–tapia A, Van Dyke CT, Brogan DL, Knipschield MA, Lahr B, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clinical Gastroenterology and Hepatology. 2008;6(2):186-93.
40. Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology. 2004;126(3):643-53.
41. Carey EJ, Leighton JA, Heigh RI, Shiff AD, Sharma VK, Post JK, et al. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. The American journal of gastroenterology. 2007;102(1):89.
42. Sidhu R, Sanders DS, Kapur K, Leeds JS, McAlindon ME. Factors predicting the diagnostic yield and intervention in obscure gastrointestinal bleeding investigated using capsule endoscopy. J Gastrointestin Liver Dis. 2009;18(3):273-8.
43. De Leusse A, Vahedi K, Edery J, Tiah D, Fery–Lemonnier E, Cellier C, et al. Capsule endoscopy or push enteroscopy for first-line exploration of obscure gastrointestinal bleeding? Gastroenterology. 2007;132(3):855-62.
44. Laine L, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial versus dedicated small bowel radiography. Gastroenterology. 2010;138(5):1673-80. e1.
45. Neu B, Ell C, May A, Schmid E, Riemann J-F, Hagenmüller F, et al. Capsule endoscopy versus standard tests in influencing management of obscure digestive bleeding: results from a German multicenter trial. The American journal of gastroenterology. 2005;100(8):1736.
46. Albert JG, Schülbe R, Hahn L, Heinig D, Schoppmeyer K, Porst H, et al. Impact of capsule endoscopy on outcome in mid-intestinal bleeding: a multicentre cohort study in 285 patients. European journal of gastroenterology & hepatology. 2008;20(10):971-7.
47. Gubler C, Fox M, Hengstler P, Abraham D, Eigenmann F, Bauerfeind P. Capsule endoscopy: impact on clinical decision making in patients with suspected small bowel bleeding. Endoscopy. 2007;39(12):1031-6.
48. Katsinelos P, Chatzimavroudis G, Terzoudis S, Patsis I, Fasoulas K, Katsinelos T, et al. Diagnostic yield and clinical impact of capsule endoscopy in obscure gastrointestinal bleeding during routine clinical practice: a single-center experience. Medical Principles and Practice. 2011;20(1):60-5.
49. Selby W. Can clinical features predict the likelihood of finding abnormalities when using capsule endoscopy in patients with GI bleeding of obscure origin? Gastrointestinal endoscopy. 2004;59(7):782-7.

50. Gilbert D, O'malley S, Selby W. Are repeat upper gastrointestinal endoscopy and colonoscopy necessary within six months of capsule endoscopy in patients with obscure gastrointestinal bleeding? Journal of gastroenterology and hepatology. 2008;23(12):1806-9.
51. Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. The American journal of gastroenterology. 2005;100(11):2407.
52. Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. Gastrointestinal endoscopy. 2011;74(1):167-75.
53. Mylonaki M, Fritscher-Ravens A, Swain P. Wireless capsule endoscopy: a comparison with push enteroscopy in patients with gastroscopy and colonoscopy negative gastrointestinal bleeding. Gut. 2003;52(8):1122-6.
54. Fork F-T, Karlsson N, Kadhem S, Ohlsson B. Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with failed and uncertain passage of a patency capsule. BMC medical imaging. 2012;12(1):3.
55. Viazis N, Zacharakis G, Saprikis E, Anastasopoulos H, Kechagias G, Markoutsaki T. A single center experience of 2300 consecutive patients undergoing capsule endoscopy: indications and diagnostic yield. Endoscopy. 2011;43:A129.

Appendix

Age:	
Gender: 1. Male 2. Female	
Co morbidities	
Indication for CE/referral diagnosis Gastrointestinal bleeding 1 Iron deficiency anaemia 2 Crohn's disease 3 Suspected small bowel tumour 4 Other –specify 5	
Presence of anaemia yes 1 No 2	
Haemoglobin (g/dl)	
Iron studies	
Findings at CE: 1. Vascular lesions (angioectasia, varices) 2. Inflammatory lesions(villous oedema, erythematous mucosa erosions, ulcers or stenosis 3. Other lesions: villous atrophy, polyps, tumours 4. Studies with normal findings 5. Inconclusive studies	
Reason for inconclusive study	
Adverse events	
Outcome:	
Death	
Cause	

Appendix 2: Ethical approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

30 October 2018

Dr N Naicker (209500943)
School of Clinical Medicine
College of Health Sciences
209500943@stu.ukzn.ac.za

Dear Dr Naicker

Protocol: Capsular endoscopy: A single centre experiences.
Degree: MMed
BREC Ref No: BE510/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 08 August 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 26 October 2018 to BREC letter dated 10 September 2018 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 30 October 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **30 October 2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 November 2018.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

Supervisor: Cassim@ukzn.ac.za Postgrad admin: konar@ukzn.ac.za

Appendix 3: Data collection tools

Age:	
Gender: 3. Male 4. female	
Co morbidity	
Indication for CE/referral diagnosis Gastrointestinal bleeding 1 Iron deficiency anaemia 2 Crohn's disease 3 Suspected small bowel tumour 4 Other –specify 5	
Presence of anaemia	Yes/No
Haemoglobin (g/dl)	
Iron studies	
Findings at CE: 6. Vascular lesions(angioectasia, varices) 7. Inflammatory lesions(villous oedema, erythematous mucosa erosions, ulcers or stenosis 8. Other lesions: villous atrophy, polyps, tumours 9. Studies with normal findings 10. Inconclusive studies	
Reason for inconclusive study	
Adverse events	
Outcome:	
Death	
Cause	