Diagnostic yield of capsule endoscopy for small bowel arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia: a systematic review and meta-analysis

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ABSTRACT

Background and study aims Small bowel arteriovenous malformations (AVMs) pose a bleeding risk and have traditionally been diagnosed by invasive enteroscopic procedures in patients with hereditary hemorrhagic telangiectasia (HHT). Capsule endoscopy (CE) is emerging as a safe and non-invasive alternative for small intestinal evaluation, but its diagnostic yield and utility in diagnosing small bowel AVMs in HHT patients are understudied. The aim of this study was to meta-analyze the utility of CE for diagnosing AVMs in HHT patients.

Methods A meta-analysis and systematic review of the literature on CE in HHT patients identified in the PubMed, EMBASE, Scopus, and Cochrane databases from inception to March 2018 were conducted. Summary effects were estimated using a random effects model.

Results After applying exclusion criteria, five studies (n = 124 patients) were eligible for meta-analysis. The pooled diagnostic yield for visualization of small bowel AVMs by CE was 77.0% (95% CI 65.8–85.4%, P < 0.001).

Conclusions CE has a good diagnostic yield for small bowel AVMs in HHT. It can be regarded as a sufficient, noninvasive diagnostic modality for identifying small bowel AVMs in HHT patients.

Introduction
Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare, autosomal-dominant syndrome characterized by multiple arteriovenous malformations (AVMs) in the mucous membranes, skin, liver, gastrointestinal tract (GIT), and brain [1]. The Curacao Criteria are often used to guide diagnosis of HHT based on the presence of key clinical features including spontaneous and recurrent epistaxis; multiple telangiectasias at characteristic sites such as the lips, oral cavity, fingers and nose; visceral lesions such as pulmonary, hepatic, cerebral, gastrointestinal, and spinal AVMs; or having a first-degree relative with HHT that meets diagnostic criteria. Patients who meet two criteria have a suspected diagnosis, while three or more criteria are diagnostic.

Small bowel bleeding has a number of causes, including erosions, ulcers, polyps, tumors, and vascular phenomena such as AVMs. GIT bleeding from small bowel AVMs is a common and important cause of mortality in HHT patients, and it is estimated that 33% of HHT patients will develop gastrointestinal bleeding during their lifetime [2]. Gastrointestinal bleeding is most commonly occult and detected as chronic iron deficiency anemia in patients with HHT, but less frequently, AVMs can produce overt, massive gastrointestinal bleeding. Prior to 2001,
the gold standard diagnostic and therapeutic interventions for small intestinal bleeding were invasive modalities such as push, intraoperative, or deep enteroscopy (spiral enteroscopy prior to 2001 and double and single balloon enteroscopy after 2001), due to their ability to visualize small bowel inaccessible to esophagogastroduodenoscopy or colonoscopy [3]. However, these modalities are not universally available, and not all endoscopists are trained to operate these enteroscopes. Furthermore, these procedures are considered invasive because patients require sedation, may require purgative bowel preparation, and the procedure itself can cause significant abdominal discomfort during and after the procedure. Capsule endoscopy (CE), a relatively noninvasive alternative for diagnosis of small intestinal gastrointestinal bleeding, involves ingesting a camera within a capsule that captures images as it traverses the gastrointestinal tract. CE is relatively inexpensive, requires less training for endoscopists, and may be more readily available than the invasive enteroscopic techniques. It is often considered noninvasive because it does not require conscious sedation and is generally well tolerated.

Because there are only approximately 5,000 to 8,000 patients with HHT worldwide [1], very few studies have examined the diagnostic value of CE for detecting small bowel AVMs in this population. To the best of our knowledge, this is the first meta-analysis of studies on the adequacy of CE for diagnosing small bowel AVMs in HHT patients. We also used this opportunity to review the therapeutic interventions that can be used in HHT patients when small bowel AVMs are identified.

Methods

The PubMed, EMBASE, Scopus, and Cochrane databases were searched from inception to March 26, 2018 according to PRISMA guidelines. Eligibility criteria were patients diagnosed with HHT who underwent CE to detect small bowel AVMs. Studies that involved children, pregnant women, and patients who did not undergo CE for evaluation of small bowel AVMs were excluded. The search criteria were “hereditary hemorrhagic telangiectasia” combined with “CE” or “arteriovenous malformations” within the titles and abstracts. Titles were then screened for exclusion criteria that would make the study ineligible, and articles were then independently selected and the abstracts and full texts reviewed by two authors (KS and AP). Any disagreements were resolved by discussion and, if a consensus had been lacking, the article would have been referred to another co-author (AN) for final adjudication. However, in this case, there were no disagreements. Bias assessment using the Cochrane tool for risk of bias assessment was also performed.

The number of patients who underwent CE and the number of subjects found to have AVMs by CE were extracted from each study. Using this information, the diagnostic yield or detection rate was calculated using the following formula: number of subjects found to have AVMs divided by the total number of subjects that underwent CE. To examine the diagnostic yield (with 95% confidence intervals [CI]) for CE detection of AVMs in HHT patients in each study, the interaction terms across studies were summarized by meta-analysis. Summary effects were estimated using a random effects model. The assumption of a constant interaction term across trials was tested for heterogeneity by examining $I^2$, $T^2$, $Q$, and $P$ values for heterogeneity. A sensitivity analysis was performed by including an additional meta-analysis using a fixed effects model. Analyses were performed in Comprehensive Meta-Analysis (CMA) version 3.2.

Results

Study selection

Of the 3,509 articles identified (Fig. 1), none were in the Cochrane database. Six studies met the eligibility criteria and evaluated use of CE to identify AVMs in patients with HHT [4–9]. One study [9] was subsequently retracted by the author and/or editor, leaving five studies for meta-analysis (Fig. 1 and Table 1).

Detection rate of small bowel AVMs by CE

In the five eligible studies, 124 patients were available for analysis (Table 1) [4–8]. Overall, AVMs were detected by CE in 77.0% of patients (95% CI 65.8 – 85.4%, $P < 0.001$) with HHT using a random effects model (Fig. 2a). In Ingrosso et al. [7], 50% of patients who underwent CE had suboptimal images, leading to inconsistency with the other studies and heterogeneity ($I^2 = 37.2$, $T^2 = 0.148$, $Q = 6.34$, and $P = 0.173$). However, when this study was excluded, the pooled diagnostic yield of CE was 81.1% (95% CI 72.4 – 87.6%, $P < 0.001$) and there was greater homogeneity ($I^2 < 0.0001$, $T^2 < 0.0001$, $Q = 1.09$, and $P = 0.78$) (Fig. 2b). The calculated prediction interval was 77.0% (95% CI 66.5 – 87.6%) when all five studies were included, while exclusion of the study by Ingrosso et al. reported a prediction interval of 81.1% (95% CI 66.8 – 95.4%). The overall results of our meta-analysis were similar in both fixed and random effects models, with the sensitivity analysis suggesting that the small sample size did not influence overall outcomes. A bias assessment was performed in accordance with the Cochrane tool for assessment of studies, and the risk of bias of these studies was consistently low despite the limitations that these studies were only prospective observational studies (Table 2).

Discussion

AVMs are abnormal communications between the arteries and veins that bypass the normal capillary bed. The pathogenesis of AVMs in HHT is not completely understood, but histopathological examination of AVMs in these patients reveals an irregular endothelium, increased collagen and actin, and a convulsed basement membrane. At the molecular level, mutations that disrupt transforming growth factor β-mediated pathways impair angiogenesis and result in overall extreme blood vessel fragility [10]. The most frequent mutations affecting these pathways include mutations in the endoglin (ENG), activin receptor-like kinase 1 (ACVRL1 or ALK1), and SMAD4 genes and consequent deficiencies in their encoded proteins. ACVRL1 and ENG are essential components of cell surface receptors for transforming growth factor-β-mediated pathways, while SMAD4...
Fig. 1 Flowchart of study selection.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th># of subjects with HHT enrolled</th>
<th>Average age (years)</th>
<th>Gender</th>
<th># of subjects included in final analysis</th>
<th>Indication of CE</th>
<th>Average small intestinal transit time (minutes)</th>
<th>Excellent adequacy of CE visibility</th>
<th>Location of small bowel AVMs¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingrosso (2004)</td>
<td>Italy</td>
<td>Prospective</td>
<td>20</td>
<td>54²</td>
<td>11 M 9 F</td>
<td>18³</td>
<td>Identification of gastrointestinal lesions</td>
<td>274⁴</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chamberlain (2006)</td>
<td>USA</td>
<td>Prospective</td>
<td>38</td>
<td>54 ± 13.2</td>
<td>18 M 14 F</td>
<td>32⁵</td>
<td>Investigation of small bowel bleeding</td>
<td>NR</td>
<td>NR</td>
<td>Proximal 17 (53%) Mid 19 (59%) Distal 20 (63%)</td>
</tr>
<tr>
<td>Van Tuyl (2006)</td>
<td>Netherlands</td>
<td>Prospective</td>
<td>25</td>
<td>49 ± 17</td>
<td>14 M 11 F</td>
<td>25</td>
<td>Anemia without a source</td>
<td>264 ± 91</td>
<td>NR</td>
<td>Ileum 21 (84%), remainder of the SB NR</td>
</tr>
<tr>
<td>Greve (2010)</td>
<td>France</td>
<td>Prospective</td>
<td>30</td>
<td>57.7 ± 11.2</td>
<td>10 M 20 F</td>
<td>27⁶</td>
<td>Anemia without a source</td>
<td>252⁴</td>
<td>50%</td>
<td>Proximal 27 (100%) Distal 15 (55.6%)</td>
</tr>
<tr>
<td>Canzionario (2014)</td>
<td>Italy</td>
<td>Prospective</td>
<td>22</td>
<td>59 ± 9</td>
<td>13 M 19 F</td>
<td>22</td>
<td>Identification of gastrointestinal lesions</td>
<td>232⁴</td>
<td>NR</td>
<td>D:18 (8.18%) J: I4 (63.6%) I:13 (59%)</td>
</tr>
</tbody>
</table>

CE, capsule endoscopy; D, duodenum; F, female; J, jejunum; I, ileum; M, male; NR, not reported

¹ Definitions for location of small bowel AVMs: Chamberlain et al., areas of small bowel were divided into proximal, mid-, and distal regions according to thirds of time of the capsule traversing the small bowel; Greve et al., areas of small bowel were divided into proximal and distal regions defined by halves of time of the capsule traversing the small bowel; Canzionario et al., areas of small bowel divided accordingly by location duodenum (D), jejunum (J), and ileum (I) by thirds of time of the capsule traversing the small bowel.

² Standard deviation not reported.

³ Two subjects excluded from final analysis because of battery dysfunction of the capsule.

⁴ Standard deviation not reported.

⁵ Two subjects were excluded from final analysis because there was incomplete capsule transit to the cecum and four were excluded because the referred patients did not have at least a possible diagnosis of HHT.

⁶ Three subjects were excluded from final analysis because there was one instance of battery failure for the capsule and two cases of capsule retention.

Table 1 Studies included in the analysis.
acts as an intermediary between the extracellular growth factors and the nuclear transcriptional machinery [11–13].

Because GIT AVMs are found in the majority of patients with HHT and gastrointestinal bleeding is more prevalent in HHT patients older than 40 years, screening for iron deficiency anemia, a possible manifestation of gastrointestinal bleeding, is recommended through serial hemoglobin or hematocrit measurements and serum iron studies after age 35 [2, 14–16]. Although significant epistaxis most frequently causes iron deficiency anemia in HHT patients, sources of bleeding from the GIT should be ruled out by endoscopy when epistaxis is absent or the degree of epistaxis is disproportionate to the degree of anemia. However, when gastrointestinal bleeding is suspected or evident, bleeding AVMs are most frequently found in the stomach or colon, so the recommended initial diagnostic assessment involves esophagogastroduodenoscopy (EGD) and colonoscopy. Prior to the introduction of CE, when a source of bleeding was not identified by EGD or colonoscopy, more inva-
sive diagnostic procedures such as push, deep, or intraoperative enteroscopy were used to rule out small bowel AVMs; however, the diagnostic yield was generally low with the exception of intraoperative enteroscopy, widely considered the most invasive modality because occasionally small bowel access may require an enterotomy site (Table 3) [17]. These invasive diagnostic modalities have now largely been replaced with the less invasive CE, even though the procedure is not therapeutic after lesion identification. Due to the rarity of HHT, the sample sizes of relevant published studies are generally small, so here we sought to assess the combined effect sizes through meta-analysis in an effort to determine whether CE provides significant diagnostic yield to identify AVMs in HHT patients. We conclude that the diagnostic yield for AVMs by CE is sufficient to diagnose small bowel AVMs in these patients.

Our findings are important because CE can identify small bowel AVMs early and map the lesions in the GIT to identify patients who may benefit from therapeutic interventions that prevent the morbidity and mortality associated with GIT bleeding. Of the numerous available therapeutic interventions, AVMs tend to be amenable to endoscopic treatments, especially with single, proximal AVMs accessible to the enteroscope. Endoscopic treatments include standard electrocoagulation or neodymium yttrium-aluminum-Garnet lasers via push enteroscopy but, since the advent of deep enteroscopy, argon plasma coagulation has become the primary therapeutic choice [3]. Also, newer hemostatic powders (e.g., Hemospray, Endoclot, and Ankafred) primarily used to control bleeding at post-polypectomy sites, diverticula, and colonic tumors are now being investigated in prospective studies as a potential therapeutic option for GIT bleeding from AVMs [18] and may be useful in the HHT population.

In some instances, therapeutic control may be difficult to attain by endoscopy, such as when multiple attempts at endoscopic hemostasis (and consequent high risk of rebleeding) have been made. Also, surgery may be considered in patients: (1) with acute severe bleeding uncontrolled by multiple attempts at endoscopic hemostasis; and (2) who have had other treatments but continue to have recurrent chronic bleeding from a clearly identified source and have become transfusion dependent; however, surgery is considered a last-line option due to the postsurgical complications that may arise [19, 20]. There are also numerous non-endoscopic, pharmacological agents that can be used as adjunct therapies, either in combination with endoscopic therapies or as monotherapy. These agents are especially useful in patients whose conditions remain refractory to or unsuitable for conventional therapies, such as those with multiple AVMs that would otherwise make endoscopic therapy challenging [4, 21]. These pharmacological options include estrogen—progestogen preparations, danazol, tamoxifen, thalidomide, lenalidomide, interferon-2β, sirolimus, octreotide, amincapric acid or tranexamic acid, and bevacizumab (Table 4) [22–24]. However, due to the rarity of HHT, significant reported adverse events (AEs) with these agents, and the poor evidence base from only case reports, case series, and small clinical trials [1, 25, 26], a thorough discussion regarding the benefits and risks of initiating such therapies should be held between provider and patient and further studies are warranted.

Choosing a drug therapy for treatment of small bowel AVMs is difficult because of the weak evidence base [16]. The most recent HHT guidelines published in 2011 by the HHT Guidelines Working Group recommended hormonal therapies or antifibrinolytic agents such as aminocaproic acid or tranexamic acid in patients receiving medical therapy [14]. Hormonal therapies have been recommended to treat AVM lesions causing chronic gastrointestinal bleeding because HHT symptoms improved during pregnancy and worsened during menopause [27]. In patients started on antifibrinolytic agents, ruling out the presence of pulmonary AVMs is critical because these agents pose a risk of thrombosis. Of note, since the publication of these guidelines, reports on treatment of AVMs in the general population with hormonal therapies have provided mixed results, with some studies demonstrating a beneficial role in decreasing red blood cell transfusion requirements and overall rebleeding rates and others and a meta-analysis suggesting that these therapies ineffectively control bleeding [28, 29]. Since the publication of these recommendations, bevacizumab, a drug extensively studied in HHT patients for treatment of epistaxis, has gained attention and is now among the most studied drugs in HHT patients with evidence of gastrointestinal bleeding in 16 case series/reports of 31 patients, four retrospective studies, and one Phase II study [30–44]. In these studies, bevacizumab decreased the frequency and severity of gastrointestinal bleeding and epistaxis, led to higher baseline hemoglobin levels, and reduced red blood cell transfusion requirements and dependency. Aside from treating GIT AVMs, bevacizumab also improved other HHT manifestations, such as multiple liver AVMs, normalized high cardiac output states, decreased biliary dilatation, resolved bilomas, normalized liver size, reduced celiac artery flow and arteriovenous shunting, lessened capsular pain and abdominal angina, and improved chronic liver disease to the point of allowing delisting of patients for liver transplantation [35].

Other frequently studied therapeutic agents include thalidomide and octreotide, both of which have demonstrated benefit in the general population to treat small bowel AVMs and, as a result, are recommended for use in the general population by the consensus opinion published by the Italian Society of Gastroenterology [29]. Octreotide reduces iron requirements and rebleeding events and improves rebleeding-free survival with-

<table>
<thead>
<tr>
<th>Diagnostic technique</th>
<th>Diagnostic yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Push enteroscopy</td>
<td>15% – 40%</td>
</tr>
<tr>
<td>Single balloon enteroscopy</td>
<td>41% – 65%</td>
</tr>
<tr>
<td>Double balloon enteroscopy</td>
<td>40% – 80%</td>
</tr>
<tr>
<td>Spiral enteroscopy</td>
<td>12% – 59%</td>
</tr>
<tr>
<td>Intraoperative enteroscopy</td>
<td>58% – 100%</td>
</tr>
</tbody>
</table>

Reported diagnostic yields for different diagnostic techniques to diagnose causes of small intestinal bleeding[17]


<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism of Action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol</td>
<td>Weak androgenic effects and direct vascular stability</td>
<td>Androgenic effects, hyperlipidemia, peliosis hepatis, hepatic adenoma, intracranial hypertension, thromboembolic events</td>
</tr>
<tr>
<td>Estrogen-progesterone</td>
<td>Vascular stability, improved coagulation, decreased mesenteric blood flow</td>
<td>Arterial and venous thromboembolism and thrombosis, hypertension, hyperlipidemia, hepatic adenoma, headaches, angioedema</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Inhibition of angiogenesis</td>
<td>Bone marrow suppression, hepatotoxicity, visual disturbances, thromboembolic events, increased risk of uterine or endometrial cancers</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal antibody directed against vascular endothelial growth factor A</td>
<td>Hypertension, heart failure, infusion reactions, arterial thromboembolism, posterior reversible encephalopathy syndrome, gastrointestinal fistula or perforation, bleeding involving the gastrointestinal tract, genitourinary tract, respiratory tract, and central nervous system</td>
</tr>
<tr>
<td>Interferon-2β</td>
<td>Inhibition of angiogenesis</td>
<td>Fever, chills, flu-like symptoms, hypothyroidism, immune-mediated hemolytic anemia, connective tissue disorders</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Inhibitor of angiogenesis through blockade of IL-6 and other pathways</td>
<td>Venous thromboembolism, Stevens-Johnson syndrome, dizziness, drowsiness, peripheral neuropathy, seizures, constipation, abnormal liver function tests, bone marrow suppression, increased risk of acute myeloid leukemia and myelodysplastic syndromes</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Inhibitor of angiogenesis through blockade of IL-6 and other pathways</td>
<td>Venous thromboembolism, Stevens-Johnson syndrome, constipation, abnormal liver function tests, bone marrow suppression, increased risk of acute myeloid leukemia and myelodysplastic syndromes, and less neurotoxic presentations than thalidomide including dizziness, drowsiness, peripheral neuropathy</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Interleukin-2 inhibitor via mTOR inhibition</td>
<td>Peripheral edema, abdominal pain, constipation, diarrhea, nausea, acne, hypertension, hyperlipidemia, and increased serum creatinine, and risk of infection, lymphoma, and leukemia,</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Decreased mesenteric blood flow</td>
<td>Abnormal Schillings test, cholelithiasis, pancreatitis, hypothyroidism</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Increased coagulation</td>
<td>Central nervous system depression, hypersensitivity reactions, visual disturbances, seizures, venous and arterial thrombosis or thromboembolism, ureteral obstruction</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>Increased coagulation</td>
<td>Intrarenal obstruction, myoglobinuria, renal failure, hyperkalemia, pulmonary embolism, skeletal muscle weakness, leukopenia, thrombocytopenia, agranulocytosis, bradycardia, arrhythmias, seizures, stroke, injection site necrosis, rashes, intracranial hypertension, peripheral ischemia, syncope, myocardial thrombosis, delirium, headaches,</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation

out significantly increasing AEs, so is considered a safe and effective option for rescue therapy in patients with actively bleeding angioectasias [29]. Thalidomide’s benefits include stopping bleeding, reducing bleeding episodes within the first year of follow-up, and improving baseline hemoglobin levels, but hepatotoxicity is not an uncommon AE, with manifestations ranging from mild transaminase elevations to decompensated chronic liver disease with hepatic encephalopathy [29]. There has yet to be a comparison of thalidomide and its analogue lenalidomide for treating small bowel AVMs [29, 45]. Use of tamoxifen, danazol, sirolimus, and IFN-2β is less well studied and they have only been described in case reports and may be reserved for patients with contraindications or who do not respond to other therapies [1, 16, 46–48].

Our study has some limitations. HHT is relatively rare, so only a limited number of studies have investigated use of CE in HHT patients with suspected small bowel AVMs and this was reflected through a broad prediction interval despite a large pooled effect size. Also, all of the available studies were small, prospective and observational and there are no randomized clinical trials. Based on our eligibility criteria, the study by Ingroso et al. was included even though the CE views were frequently suboptimal, which is likely to have affected the overall diagnostic yield. Together, these factors may have contributed to effect size heterogeneity; indeed, exclusion of the Ingroso et al. study increased homogeneity. Although exhaustive and concerted efforts were made, we did not find any unpublished studies, and our meta-analysis may have suffered from publication bias. Lastly, many of the enrolled patients did not have active gastrointestinal bleeding and because CE has the highest diagnostic yield during active bleeding, the diagnostic yield in these studies may have been underestimated.

**Conclusion**

In conclusion and despite its limitations, our meta-analysis revealed that CE is a safe, noninvasive, and inexpensive diagnostic modality to diagnose and map AVMs along the GIT in patients with HHT. Although no studies compared the diagnostic yield of CE versus invasive enteroscopy to diagnose AVMs in this pop-
ulation, our findings suggest that CE is a useful alternative to invasive enteroscopy for diagnosing AVMs in patients with HHT. Studies in the general population suggest that therapies started after CE increased hemoglobin levels and reduced risk of rebleeding, transfusion requirements, the number of gastrointestinal procedures performed, and the duration of hospitalization [49–55]. Hence, when AVMs are identified, endoscopic, surgical, and medical AVM therapies can be considered and decisions can be made according to the mapped locations of AVMs. Due to the heightened risk of gastrointestinal bleeding and mortality in HHT patients and current guidelines recommending against treating non-bleeding small bowel AVMs in asymptomatic patients in the general population, additional studies should focus on whether there is clinical benefit to early treatment of asymptomatic AVMs in HHT patients. If there is demonstrable benefit, CE may not only serve as an important diagnostic modality in HHT patients but may also become an important screening tool to prevent morbidity and mortality associated with GI bleeding [3, 56, 57].

Competing interests

None

References

Singh Kevin et al. Diagnostic yield of ... Endoscopy International Open 2019; 07: E282–E289


