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Role of octreotide in small bowel bleeding

Khedr A *et al.* Octreotide in small bowel bleeding

Abstract

Gastrointestinal bleeding accounts for a drastic ⁷ negative impact on the quality of the patients' lives as it requires multiple diagnostic and therapeutic interventions to identify ¹¹ the source of the bleeding. Small bowel bleeding is the least common cause of gastrointestinal bleeding. However, it is responsible for the majority of complaints from patients with persisting or recurring bleeding where the primary source of bleeding cannot be identified despite investigation. A somatostatin analog known as octreotide is among the medical treatment modalities currently used to manage small bowel bleeding. This medication helps control symptoms of gastrointestinal bleeding by augmenting platelet aggregation, decreasing splanchnic blood flow, and antagonizing angiogenesis. In this review article, we will highlight the clinical efficacy of octreotide in small bowel bleeding and its subsequent effect on morbidity and mortality.

Key Words: Octreotide; Small bowel; Hemorrhage; Angiodysplasia; Vascular malformations; Hereditary hemorrhagic telangiectasia

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Core Tip: Small Bowel bleeding can result from vessel malformations, inflammation, varices, drugs, infections, tumors, or coagulopathy disorders. Octreotide, a synthetic somatostatin analog, is an effective therapy in stopping esophageal variceal bleeding by causing splanchnic vasoconstriction. Octreotide can also be used to control small intestinal variceal bleeding depending on similar mechanisms. Using Octreotide in

treating other non-variceal etiologies of small gastrointestinal bleeding has been evaluated and reported with promising results.

INTRODUCTION

Gastrointestinal (GI) bleeding negatively impacts patients' health, and locating the source of these bleeds can be time-consuming^[1]. Small bowel bleeding is the least common location of all GI bleeds, making up only 5%-10% of total GI bleeds. However, these lesions are difficult to diagnose in patients and can be challenging to identify^[2].

Small bowel bleeding can be defined as uncontrolled hemorrhage of the bowel located in a region of the GI tract that spans from the ligament of Treitz to the start of the ileocecal valve^[3]. The etiology of small bowel lesions is widespread, including vascular, those secondary to inflammation, and tumors, amongst other causes^[4]. Additionally, clinicians must also consider the potential infectious or drug-induced etiologies for small bowel bleeding as well^[2]. Lesions of the small bowel and their etiology significantly depend on the individual's age. In the elderly age group, small bowel bleeds are usually attributed to vascular lesions, like angioectasias, with vascular lesions making up 30%-40% of bleeding in the small bowel in all age groups^[2]. Younger patients commonly have small bowel bleeds from Crohn's disease or Meckel's diverticulum. Gender holds no significant role, with prevalence equal in men and women, indicating no strong link between gender and the occurrence of small bowel bleeds^[2]. Those who present with small bowel bleeding typically require several diagnostic procedures which can delay care and result in inappropriate therapy. Which is why identifying the cause and site of bleeding is vital for appropriate management^[4]. As small bowel bleeding is particularly difficult to diagnose, as currently, there is no diagnostic tool that can reach the small intestine appropriately^[2].

Octreotide is a synthetic polypeptide similar to somatostatin in structure and pharmacological function^[5]. Like somatostatin, octreotide suppresses the secretion of growth hormone and thyrotropin from the anterior pituitary gland, in addition to decreasing the release of certain pancreatic islet cell hormones such as insulin,

glucagon, and vasoactive peptide (VIP)^[5]. Octreotide has additional functions: Reducing splanchnic blood flow, secretion of gastric acid, GI motility, exocrine pancreatic function, and altering water, nutrient, and electrolyte absorption from the GI tract. The clinical use of octreotide is seen in GI and endocrine systems disorders. One of the main uses of octreotide is treating and managing carcinoid tumors. Octreotide suppresses severe diarrhea/flushing associated with carcinoid tumors and manages potentially life-threatening hypotension in carcinoid crisis^[5]. Additionally, octreotide can be used to manage watery diarrhea in VIP-secreting tumors, and it can reduce growth hormone and insulin-like growth factor concentrations in patients with acromegaly^[5]. Recently, octreotide has been shown to be an effective therapy in treating GI bleeding in patients with poor responses to previous treatments^[6,7]. The common adverse effects of octreotide include diarrhea, abdominal pain, flatulence, steatorrhea, vomiting, cholelithiasis, biliary sludge, sinus bradycardia, conduction abnormalities, and arrhythmias^[5].

This paper aims to elucidate the role of octreotide in treating small bowel bleeding in different diseases and presentations. This review provides a brief overview of octreotide and its traditional uses. We also review the different studies that demonstrated octreotide's role in treating different small bowel bleeding presentations in angiodysplasia, blue rubber bleb nevus syndrome (BRBNS), hereditary hemorrhagic telangiectasia (HHT), intestinal varices, and left ventricular assist device (LVAD)-associated GI bleeding. We searched PubMed and Google Scholar and selected relevant articles. Keywords such as octreotide, Small bowel, hemorrhage, angiodysplasia, vascular malformations, HHT, BRBNS, and LVAD-associated GI bleeding were searched individually or in combination to yield relevant information. We did not have any date or language restrictions. References of relevant articles were searched to find any missing articles not identified by our search. Duplicated studies and studies providing insufficient and irrelevant information were excluded from our review.

GASTROINTESTINAL ANGIODYSPLASIA

The GI tract is a common site for blood vessel malformations. These irregularities can lie in the arterial, venous, or capillary^[8]. Vascular anomalies can be benign like hemangiomas or malignant like angiosarcomas. These aberrations can also be hereditary, such as HHT, or acquired like angiodysplasia, gastric antral vascular ectasia (GAVE), and Dieulafoy's lesion^[8,9]. Angiodysplasia is considered the most common vascular malformation found in the GI tract in the general population^[9].

Pathogenesis

The exact pathophysiology behind angiodysplasia is yet to be established, but there are proposed risk factors and associations. Impaired arterial flow, intermittent submucosal venous obstruction due to increased contractility at the level of muscularis propria, and local hypoxemia that leads to vascular degeneration and formation of small arterio-venous collaterals have been recognized as potential etiologic factors^[9,10].

Clinical presentation

Angiodysplasia has a spectrum of clinical presentations. In the general population, angiodysplasias are usually detected in patients older than 60, while chronic kidney disease (CKD) patients can be diagnosed at an earlier age^[11]. It may present with signs of GI bleeding such as unexplained iron deficiency anemia, melena, hematochezia, and positive occult blood test. Other patients can go completely asymptomatic^[12]. On rare occasions, angiodysplasia presents with life-threatening GI bleeding^[13].

Comorbidities

Angiodysplasia is counted as the most common cause of GI bleeding in the elderly age group^[14]. This can be linked to the aging process in which the GI wall is challenged by repeated episodes of high tension and fragile supporting connective tissue due to deficiency of collagen type IV, resulting in an increased incidence of angiodysplasia among the elderly^[15]. Similarly, aortic stenosis is more common in the elderly population, as it is also associated with the aging process. Moreover, an association

between these two aging processes, aortic stenosis and angiodysplasia, was first established by Dr. Edward C Heyde back in 1958^[16]. This association was labeled as Heyde's syndrome, a multisystem disorder in which the patient will present with a triad of aortic stenosis, anemia related to GI bleeding from angiodysplasias, and acquired coagulopathy (von Willebrand disease)^[17].

¹⁸ The prevalence of angiodysplasia as a cause of GI bleeding among patients with CKD ranged from 19% to 32% compared to 5% in patients with normal kidney functions^[11]. Moreover, GI bleeding ⁵ is a significant cause of morbidity and mortality in CKD patients. Angiodysplasia is also regarded as one of the most common causes of recurrent bleeding among CKD patients^[11,18]. The association between CKD and angiodysplasia is not well-known, but the increased risk of bleeding that happens in CKD could be because of uremia-induced platelet dysfunction and the use of anticoagulants^[19,20].

Diagnosis

Microscopically, angiodysplasia is described as a tortuous, ectatic, dilated, and small (2-10 mm) blood vessel ⁶ lined by endothelium with little or no layer of smooth muscle, seen in the mucosa and submucosa of the GI tract^[9,21]. Endoscopy and colonoscopy are considered the best modalities to diagnose angiodysplasias, with an estimated colonoscopy sensitivity and positive predictive value of 80% and 90%, respectively^[22]. Another imaging modality that can be used for diagnosis is wireless capsule endoscopy (WCE), which also happens to be the best imaging modality to visualize the ³⁶ small bowel in the context of obscure GI bleeding^[9]. Other imaging techniques include radionuclide scanning, magnetic resonance (MR) angiography, computed tomography (CT), and standard angiography. These radiographic imaging techniques are only useful ⁶ in the setting of active overt GI bleeding^[9]. ⁴ In a retrospective study done by Nishimura *et al* among 13 patients diagnosed with colonic angiodysplasias, the endoscopic appearance of angiodysplasias in 10 patients was visualized as flat, red spots lesions. At the same time, in the remaining patients, the lesions also appeared flat

and red with concurrent small veins that have a fern-like pattern^[23]. Although angiodysplasias can be easily seen by endoscopy, they are usually difficult to diagnose in pathologic specimens^[21].

Management

Angiodysplasia is usually an incidental finding that is seen during endoscopy^[21]. Accordingly, the decision to manage this lesion depends on the clinical context in which the angiodysplasia was diagnosed. For example, if angiodysplasia was an incidental finding in a patient with no history of GI bleeding or unexplained iron deficiency, usually no treatment is required. However, since this risk of future angiodysplasia-related bleeding is unspecified, the decision to proceed with treatment depends mainly on the expert's opinion^[21]. Angiodysplasia's management approach can broadly be divided into endoscopic, surgical, and pharmacologic. Endoscopic therapies encompass the following different techniques: argon plasma coagulation, ablation, electrocoagulation, endoclips and band ligation, and injection sclerotherapy^[9,21]. The surgical approach is reserved for cases that present with acute, severe bleeding that is uncontrolled by alternative treatment modalities or chronic cases that are transfusion-dependent and failed other treatment methods^[24]. Pharmacological therapy is safer, non-invasive, and more cost-effective approach for patients with multiple comorbidities and a high risk of complications from endoscopy^[9].

Octreotide and angiodysplasia

As a long-acting somatostatin analog, octreotide impedes and prevents bleeding from angiodysplasia lesions *via* multiple mechanisms of action. Octreotide decreases duodenal and splanchnic flow^[25], increases vascular resistance^[26], inhibits the secretion of pepsin, gastrin, and acid secretion^[27], enhances platelets aggregation^[28], and inhibits angiogenesis by suppressing VEGF production^[29]. Different types of studies, from clinical trials to observational studies, were conducted to evaluate the effect of

octreotide on patients with angiodysplasia. Additionally, several published cases reported the effects of octreotide in these patients.

A clinical trial by Nardone *et al*^[30] was conducted on seventeen patients with multiple comorbidities. Fourteen patients had angiodysplasias and three patients had diffuse antral vascular ectasias diagnosed by endoscopy. Patients were given octreotide at a dose of 0.1 mg three times daily subcutaneously for six mo. Octreotide showed a successful increase in the average hemoglobin levels from 5.7 g/dL to 11.1 g/dL and a decrease in the blood units transfused from 8.8 units to 1.5 units per year. Since this medication significantly improved the clinical outcome of vascular malformations among this study group, researchers in this study recommended the use of octreotide, especially in elderly patients who are not candidates for surgery or have other comorbidities^[30]. Another trial included thirteen patients diagnosed with iron deficiency anemia and angiodysplasia as the only known source of chronic GI bleeding^[31]. Patients were given subcutaneous (SQ) long-acting octreotide 10 mg per month. After a mean follow-up of 33 mo, the results yielded showed that these patients' hemoglobin was maintained, with a median of 13 g/dL vs 7 g/dL ($P = 0.002$), along with a significant decrease in the blood transfusion requirements, iron supplementations, and the number of hospitalizations among these patients^[31]. A different clinical trial involved fifteen patients diagnosed with refractory GI angiodysplasias who were given long-acting somatostatin analogs monthly for a median of 12 mo^[32]. This study further proved that long-acting somatostatin analogs might represent a treatment option for GI angiodysplasias as the medications successfully decreased the blood transfusions rate (median = 2) compared to a median of 10 before treatment ($P \leq 0.001$), and the bleeding events happened among 20% of the patients compared to 73% ($P = 0.01$) before starting the treatment. Additionally, the hemoglobin levels were higher after somatostatins were started with a median of 10 g/dL vs 7 g/dL before treatment ($P < 0.001$)^[32]. A more recent clinical trial was conducted on 24 patients with refractory small bowel angiodysplasia to assess the efficacy of long-acting somatostatin analogs. After giving at least three doses of 20 mg

8 of long-acting octreotide for a minimum of 3 mo to 20 out of 24 patients, the average hemoglobin levels 8 increased from 9.19 g/dL to 11.35 g/dL ($P = 0.0027$). Moreover, 70% 6 ($n = 14$) of the patients remained transfusion-free after a mean treatment duration of 8.8 mo^[33]. Clinical trials that evaluated the efficacy of octreotide in patients with angiodysplasia are summarized in Table 1.

A retrospective study was conducted by Nardone *et al*^[34] on 98 patients that were diagnosed with angiodysplasia lasting for two years or more. The patients in this study were given one cycle of octreotide, which is 0.1 TID for 28 d, 12 and then starting from day 14, long-acting release octreotide 20 mg was also introduced for 6 mo. After a median follow-up of 78 mo, all patients showed a remarkable rise in the hemoglobin levels and a significant 9 decrease in the number of blood transfusions, bleeding episodes, and hospitalization 12 compared to the two years observation period before initiating the somatostatin analog^[34]. In another observational study by Salgueiro *et al*^[35], 16 patients with multiple GI vascular lesions, including angiodysplasia, were involved in the study. Among these patients, nine patients received 10 mg of long-acting repeatable (LAR) octreotide LAR per month, while the remaining received 20 mg/mo of octreotide LAR for a median time of 12 mo. A significant drop in the number of hospital admissions and blood transfusions was noticed among 14 patients. The remaining two struggled with the adverse effects of the medication (gallstones and splenic infarction), and octreotide was discontinued. There were no clinical differences between the groups that received 10 mg/mo vs 20 mg/mo^[35]. Interestingly, a study was conducted to determine 21 the efficacy of octreotide in stopping GI bleeding related to AVMs among 38 30 patients with atrial fibrillation who were also receiving oral anticoagulants for stroke prevention^[36]. These patients were given ten micrograms of octreotide subcutaneously twice daily for a median duration of 8 mo. Among 28 patients who continued oral anticoagulants out of 36, 19 had no 21 recurrent GI bleeds, 4 had minor GI bleeds, while the remaining 5 had major GI bleeds. Additionally, the levels of hemoglobin among the 28 patients 10 were significantly higher at 3 mo (9.33 g/dL vs 7.49 g/dL; $P \leq 0.001$) and at 6 mo (11.10 g/dL vs 7.49 g/dL; $P \leq 0.001$) compared to the baseline^[36].

⁴ A systematic review and an individual patient meta-analysis conducted by Goltstein *et al*^[37] discussed the effectiveness of somatostatin analogs in GI bleeding due to angiodysplasia, and this review encompassed 11 studies and analyzed 212 patients. The results showed a significant decrease in the red blood cell transfusions from the baseline of 12.8 [95%CI: (10.4-15.8) to 2.3 (1.9-2.9), $P < 0.0001$] during a median treatment duration of 12 mo. This review also showed that the angiodysplasias in the stomach had a worse treatment response than those in the small bowel and colon^[37]. In another systemic review and meta-analysis, the efficacy of somatostatin analog among four studies illustrated a pooled odds ratio of 14.5 (95%CI: 5.9-36.0) for stoppage of bleeding in patients with GI angiodysplasia^[38].

¹ In a case report, a 54-year-old female, a known case of chronic renal failure due to suspected sarcoidosis, presented with severe and recurrent small bowel bleeding due to multiple intestinal angiodysplasias. Over the years, these bleeding episodes required multiple hospital admissions and blood transfusions (> 200 units). Eventually, her treating physicians started her on octreotide LAR 30 mg and prednisolone 60 mg three times weekly. Surprisingly, a follow-up double-balloon enteroscopy showed the resolution of all intestinal lesions detected four mo prior to the start of octreotide treatment, and the hemoglobin level was maintained at around 90 g/dL, so she did not require further treatment transfusions^[39]. Another case report presented a 72-year-old male with a known case of severe calcified aortic stenosis, hypertension, coronary artery disease, and CKD with multiple angiodysplasias in the jejunum, resulting in relapsing enterorrhagia and progressive anemia. As he was given octreotide 20 mg monthly for two years, his hemoglobin levels were stable at 11 g/dL compared to 7.2 g/dL before the treatment. Also, there was no GI bleeding relapse^[40]. Additionally, several case reports documented the significant improvement in patients' hemoglobin levels and decreased hospitalizations and blood transfusions among the patients with hemorrhagic gastrointestinal vascular malformations after initiating octreotide^[41-43].

Cost-effective analysis

A retrospective study was done to assess the long-term effects of octreotide LAR and the cost-effectiveness of this medication. This study involved 19 patients who received octreotide LAR injections between 2008 and 2013 as a treatment for recurrent GI bleeding. Most of the patients in this study received octreotide at a dose of 10 micrograms on a monthly basis. The use of octreotide showed a statistically significant reduction in the number of blood transfusions from 11.19 to 2.55, $P = 0.001$, along with increased hemoglobin levels from 6.90 g/dL to 10.62 g/dL, $P = 0.0001$. The mean annual cost of the treatment before introducing octreotide LAR was 36072.34 euros per patient (ranging from 1610.49 to 122840.50, SD 35975.22). Interestingly, the mean annual costs dropped significantly to 12867.57 € (ranging from 7371.96 € to 36891.64 €, SD 4453.02 €). Despite the fact that octreotide injections tend to be expensive, around 820.15 € per dose in the presentation of 10 micrograms, octreotide resulted in a 61.5% ($P = 0.01$) reduction in the mean cost.

BRBNS

BRBNS is a rare condition in which congenital malformation of venous tissue results in dilatation of veins throughout the body, such as the central nervous system, liver, spleen, heart, eye, and of particular importance, the small bowel^[44]. Individuals with this condition are at increased risk of spontaneous hemorrhage from venous malformations, especially in the small bowel, which can result acutely in GI bleeding and chronically in iron deficiency anemia^[45]. The presentation of this syndrome can vary; however, some present with cutaneous lesions and others with internal bleeding. Based on severity, presenting concern mainly determines how the condition is initially treated^[46].

As stated, this condition is rare. There are approximately 200 cases of this condition currently reported in medical literature^[46]. Regarding frequency and race, this condition most frequently affects White individuals^[47]. There is also an equal frequency of diagnosis between males and females^[47]. The etiology of BRBNS is commonly sporadic in origin, although recently, somatic mutations have been discovered that can also

cause this disorder *via* mutations in TIE2 (angiopoietin-1 receptor), a tyrosine kinase receptor on endothelial cells that functions for angiopoietins^[48]. These mutations are double mutations in the TEK gene, whose receptor is involved in the genesis of new blood vessels. This receptor is constitutively active in BRBNS, leading to the development of numerous venous malformations in patients^[49]. The skin lesions associated with this syndrome most commonly appear near birth, whereas the GI lesions appear later in development, near adulthood^[47]. GI lesions are rarely acutely life-threatening but can result in chronic iron-deficiency anemia that requires recurrent blood transfusions as treatment^[50]. Treatment of these lesions has not been curative to date. Options for treating the syndrome have involved iron repleting, blood infusion to treat the anemia, and surgery to remove the blebs, most of which will recur^[50]. Many drugs have been studied for pharmacologic treatment of the syndrome. This includes antifibrinolytics, sirolimus, propranolol, corticosteroids, interferon-alpha, thalidomide, and octreotide, all of which function in general to reduce the amount of hemorrhage in patients, as they have previously been used for other vascular malformations^[51].

Octreotide's use in BRBNS was shown to be effective in managing recurrent GI bleeds. Of particular interest, octreotide stops GI hemorrhage through its mechanisms of decreasing mucosal blood flow to the GI system and inhibiting acid and pepsin secretion, which prevents resolution of clots formed at sites of bleeding^[52]. One case study by Gonzalez *et al*^[53] stated that octreotide might be beneficial to use prior to surgery or in place of surgery as conservative management of the venous malformations. In another case study by Bonaventura *et al*^[54], an old anticoagulated patient on warfarin due to chronic atrial fibrillation was diagnosed with BRNBS after presenting with chronic severe anemia and fever. He was managed with long-acting octreotide acetate along with blood transfusion, hydration, and antibiotics. The patient did not have any acute GI bleeding afterward, and his hemoglobin levels improved at a three-month follow-up. Additionally, it has been described that ¹⁵the use of octreotide in the management of GI bleeds may aid in decreasing the perfusion of splanchnic blood

to the area of hemorrhage, which could result in less need for blood products in patients with BRBNS^[45].

HHT

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HHT, also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular disorder that causes classic symptoms of recurrent epistaxis, telangiectasias involving skin and mucosal membranes (including the GI tract), and iron deficiency anemia^[55]. Additionally, patients with HHT have arteriovenous malformations (AVMs) of the hepatic, pulmonary, or cerebral circulations. About one-third of individuals experience recurrent GI tract hemorrhage, with the onset being around the fifth or sixth decade of life. The recurrent hemorrhages are due to telangiectasias occurring in the duodenum, although they can also appear in the stomach and colon. The prevalence of HHT is approximately 1:5000-1:8000 individuals^[55]. There is a higher prevalence in specific geographically isolated populations, such as 1:1330 in Afro-Caribbean residents of Curacao and Bonaire^[56]. HHT is commonly under-reported since many patients are often unaware of their diagnosis or have their diagnosis overlooked at the time of admission^[57].

HHT has different subtypes and associations with several pathogenic genes involved in the TGF- β signaling pathway, such as ENG (associated with HHT1), ACVRL1 (associated with HHT2), and SMAD4 (associated with juvenile polyposis-HHT overlap syndrome)^[58]. The classical features of HHT are strongly associated with a variant in ENG or ACVRL1 but can be seen in patients with HHT1, HHT2, or JPHT^[59]. ¹⁹ Pulmonary and cerebral AVMs seem to be more common in HHT1^[60]. However, Hepatic AVMs, hepatic AVM-associated pulmonary hypertension, and pulmonary arterial hypertension are more common in HHT2^[60]. These genes encode proteins involved in the TGF- β signaling pathway, which is required for the proper development of arteriovenous structures, and each variant leads to disruptions in vascular remodeling and blood vessel wall integrity^[58]. These disruptions can lead to vascular lesions, such as AVMs, arteriovenous fistulas, and telangiectasias^[55].

Previous therapies and octreotide treatment

Most patients with HHT only experience the classic symptoms, but some patients have more severe manifestations primarily related to the recurrent nose and GI bleeding^[55]. The hemorrhagic symptoms can be managed conservatively with iron supplementation, but some patients with severe manifestations can become transfusion-dependent^[55]. Endoscopic coagulation therapy is effective for controlling active GI bleeding related to telangiectasis, but there are many challenges involved in these procedures, such as multiple bleeding sites and restricted access to the small bowel^[6].

Octreotide has been recently³ shown to be an effective therapy in treating recurrent GI bleeds secondary to telangiectasias in patients with poor responses to traditional therapies. In HHT patients, the role of octreotide is believed to be related to its function as a VEGF inhibitor^[7]. A case report of HHT treated with SQ octreotide described a 74-year-old male who was¹ diagnosed with HHT at age 9^[6]. The patient had chronic anemia due to GI bleeding, which required recurrent endoscopic ablations, iron replacement, and blood transfusions. The endoscopic procedures were insufficient in controlling his bleeding, and he suffered from anemic symptoms regardless of the iron supplementation and transfusions. After he began octreotide treatment, the patient did not require endoscopic interventions for over six mo, as compared to needing three interventions the six mo prior to starting treatment, and he required his first endoscopic intervention after approximately 13 mo. A prospective case series in 2019 investigated the safety and efficacy of octreotide for GI bleeding in HHT patients^[7]. The trial showed that octreotide-treated patients needed much fewer RBC units for transfusion than the six mo prior to treatment^[7]. An additional case report in 2011 demonstrated the effective use of octreotide to manage GI bleeding in an HHT patient^[61].

ECTOPIC INTESTINAL VARICES

¹⁴ Ectopic Varices is a term used to describe dilated portosystemic collateral veins located in sites outside the gastroesophageal area^[62]. Ectopic varices are a representation of

portosystemic shunts that are normally collapsed, but for instance, in portal hypertensive patients, the portosystemic collaterals open to reduce the intrahepatic vascular resistance^[63]. Ectopic varices account for approximately 5% of variceal bleeds that can present with hematochezia, hematemesis, or iron deficiency anemia due to Obscure GI bleeding^[64]. In addition, they are usually challenging to manage. In some cases, they are associated with high mortality, even though most of the information available regarding this topic in the literature is extracted from case series, case reports, or mini-reviews^[62]. Ectopic varices were found to be associated with portal hypertension, venous malformation, hepatocellular carcinoma, abdominal vascular thrombosis, and abdominal surgeries^[62].

In a research study that involved 169 patients with ectopic varices, 17% of the lesions were found in the duodenum, 17% in the jejunum or ileum, 14% in the colon, 9% in the rectum, and 8% in the peritoneum^[65]. In literature, small intestinal varices involve varices found in both jejunum and ileum^[64], and these varices can be concomitantly seen with intrahepatic portal hypertension and in some cases with previous abdominal surgeries^[66].

Diagnosis

Ectopic varices can be difficult to pinpoint, particularly if the varices lie in the small bowel^[62]. The presence of ectopic varices should be strongly considered in patients with a history of liver cirrhosis or portal hypertension, specifically if upper and lower endoscopy fails to localize the source of bleeding. Although its significance in acute bleeding is minor, elective capsule endoscopy has helped detect jejunal and small intestinal varices^[67]. Likewise, push enteroscopy and double-balloon enteroscopy have also been used to visualize small bowel varices^[68].

Management and role of octreotide

There are no approved management guidelines for ectopic variceal bleeding; however, we extrapolate the data established to manage esophageal varices^[64]. Patients who

present with acute ectopic variceal bleeding should be first resuscitated by replacing the intravascular volume loss with crystalloids and packed red blood cells^[64]. Endoscopic management is recommended once the patient is hemodynamically stable. Among the endoscopic techniques used are band ligation and sclerotherapy^[69,70]. A randomized trial was done to compare the efficacy of terlipressin combined with nitroglycerin vs. octreotide in a setting of acute variceal bleeding in cirrhosis^[71]. In the study, 87 patients were divided into two groups. The first group included 41 patients that received intravenous terlipressin and transdermal nitroglycerin, and the second group included 46 patients that received a continuous intravenous infusion of octreotide. After 12 h, bleeding was controlled in 59% of the patients in the first group but in 78% of the patients in the second group. Also, the mean transfusion rate was higher in the first group (three blood units) compared to a lower mean (one blood unit) for the second group. Accordingly, researchers in this study recommended the use of octreotide to control variceal patients in cases of portal hypertension due to liver cirrhosis^[71]. The management of small intestinal varices bleeding is not well established, but different treatment modalities like endoscopic ligation, selective embolization, sclerosing therapy, and transjugular intrahepatic portosystemic shunt (TIPS) have been used^[72]. In a case report, two patients who were diagnosed with intestinal variceal bleeding received octreotide over a span of 74 mo and 27 mo, respectively. The treatment was effective in preventing recurrent episodes of GI bleeding^[73]. Another study reported a case of an 81-year-old female who presented with hematochezia and was diagnosed with small bowel varices that were caused by compression of the superior mesenteric vein due to a large pancreatic neuroendocrine tumor^[74]. The patient was treated medically with propranolol, octreotide, and radiation therapy, as a surgical approach was not feasible in this case. After six mo of medical therapy, the patient did not report any bleeding episodes^[74].

LVAD-ASSOCIATED GI BLEEDING AND ROLE OF OCTREOTIDE

Mechanism of LVAD-associated GI bleeding

Heart transplantation has remained the most definitive therapy for advanced Heart Failure by improving short- and long-term outcomes. However, due to the reduced numbers of available heart donors, LVADs have been implanted at an increasing rate to help restore partial normal function^[75]; however, the need to evaluate the impact of these interventions on other systems is crucial. Although there is no limit for using LVADs in any age group, young age has been associated with an increased survival rate compared to old age after 1 and 2 years^[76].

Homeostasis dysregulation has been observed in many of these patients. Shrode *et al*^[77] reported GI bleeding and thrombosis as serious side effects of these implants. Numerous theories have emerged to explain the risk of bleeding in patients with LVAD implants. The lysis of vWF molecules due to the sheer force created by the implant has been a widely discussed mechanism. vWF multimers play a significant role in platelet aggregation and adhesion, so acquired deficiency caused by the lysis can lead to bleeding tendency. In Vitro, When shear forces were applied to vWF multimers, Baldauf *et al*^[78] observed unfolding and exposure of the A2 site on the multimer facilitating proteolytic cleavage and destruction.

Ristocetin can induce interaction between the platelet glycoprotein complex and vWF molecules, causing platelet aggregation^[79]. In a study conducted by Klovaite *et al*^[80], patients with LVAD had markedly impaired ristocetin-Induced vWF aggregation test that normalized after heart transplantation. vWF levels have returned to normal after removing the LVAD implant and undergoing heart transplantation, so Uriel *et al*^[81] reported a possible association between LVAD and a reversible acquired vWF deficiency.

Volume displacement pumps, used in earlier stages of LVADs, mimic the normal cardiac cycle by allowing filling before ejection, creating a pulsatile flow. Continuous flow LVAD (CF-LVAD), which functions at a constant speed rate, has widely replaced Volume displacement pumps^[82]. Although continuous CF-LVAD has a more beneficial effect than pulsatile LVAD and improved mortality rates in cardiac patients, normal

pulse motion is lost in CF-LVAD^[83]. Letsou *et al*^[84] observed a narrow arterial valve opening and a low pulse pressure in these patients that mimic aortic stenosis dynamics.

GI bleeding has also been associated with aortic stenosis. Patients with aortic stenosis are at higher risk of developing angiodysplasia, which presents with GI bleeding. Dysregulated angiogenesis is mediated by Angiopoietin-2 and the expression of tissue factors, which facilitates the proliferation of the blood vessels' endothelium. Tumor necrosis factor- α , which is elevated in LVAD recipients, has a leading role in releasing these mediators. This abnormality can contribute to the formation of angiodysplasia and AVMs, which cause GI bleeding^[85].

Octreotide's mechanism in the treatment of LVAD-associated GI bleeding

Vasoactive Intestinal Peptide hormone, which causes significant mesenteric vasodilation, is downregulated by somatostatin hormone. Octreotide works as a synthetic Somatostatin analog and decreases blood flow to the Gastrointestinal system.

Chan *et al*^[86] reported that octreotide could decrease endothelial nitric oxide levels, inhibiting the release of glucagon, a potent vasodilator, leading to splanchnic vasoconstriction and reduced bleeding. And for that mechanism, octreotide has been widely used in the treatment of variceal GI bleeding and explored in other non-variceal GI bleeding.

Multiple angiodysplastic lesions have been reported in patients with LVAD-associated GI bleeding. Nardone *et al*^[30] reported that Octreotide inhibits the release of endothelial growth factors that cause dysregulated angiogenesis and the formation of angiodysplasia. Kutz *et al*^[87] noticed a significant decrease in acid production, pepsin release, and GI motility after using octreotide. This beneficial effect can help in protecting friable GI mucosa and limiting the bleeding.

Effectiveness of octreotide therapy in LVAD-associated GI bleeding

In many case reports and series, octreotide was shown to be effective in stopping GI bleeds in patients after LVAD implantation. Fischer *et al* described a patient with LVAD

who suffered rising angiodysplastic lesions that were not accessible by endoscopy and caused severe GI bleeding. This patient required multiple blood transfusions after two mo of the implant. After receiving octreotide SQ injections and vWF concentrate infusions, the bleeding improved, and he was discharged without further complications^[88]. Renzo *et al* reported a case series of seven patients who suffered GI bleeding events and underwent multiple endoscopic treatments, reduced anticoagulant dosage, and proton pump inhibitors therapy to control the bleeding. They received either octreotide SQ injections or LAR depot. Six out of seven patients reported marked improvement in GI bleeding course, red blood cells transfusion, number of readmissions, and endoscopic treatments^[89]. In another case report, a patient had severe angiodysplasia causing recurrent life-threatening intestinal bleeding that occurred after the LVAD implant. Monthly IM octreotide therapy was started. The patient had a 23-mo bleeding-free period^[90]. Dang *et al*^[91] reported a patient with a HeartWare LVAD who suffered acute anemia symptoms without visible bleeding on endoscopy despite multiple blood transfusions. After starting the patient on SC octreotide twice daily, her Hemoglobin levels were stable for over three weeks. However, hemoglobin levels started decreasing later, and multiple erosions were visible on endoscopy. The patient was prescribed continuous SC octreotide and was discharged with stable hemoglobin for 2 mo^[91].

In multiple observational studies, octreotide was ¹ associated with significant morbidity and mortality reduction in patients with LVAD implants, as summarized in Table 2. In a retrospective chart review, Hayes *et al*^[92] reported that five patients who experienced LVAD-associated GI bleeding have been improving and restarted their antiplatelet or anticoagulation medications after receiving continuous infusion of Octreotide, SQ injections, ³ or monthly depot LAR octreotide for 10 d to 69 d. In a larger retrospective study, 101 patients with Heart Mate II implants were analyzed to assess the incidence, causes, and possible management of GI bleeding. Older patients above 70 years reported a higher bleeding rate. Upper GI bleeding was the predominant site with a 57% compared to lower GI Bleeding 35% bleeding rate. Traditional management plans

such as decreasing anticoagulant dosages, Blood transfusions and lowering the implant speed reduced the bleeding episodes. Nevertheless, octreotide therapy was reported not to affect bleeding events or mortality rates in these patients^[93].

Octreotide use as secondary prophylaxis for LVAD-associated GI bleeding

In a multicenter prospective cohort study, 34 patients with a history of LVAD-associated GI bleeding episodes were discharged with depot octreotide injections and SC octreotide prophylaxis and followed up to assess rebleeding event rate. Only ten patients reported bleeding episodes on average two mo after discharge. They found that a history of GIB prior to LVAD implant and sildenafil use could be risk factors for rebleeding in LVAD patients. Long-acting monthly depot injections showed a reduced bleeding rate (29%) than short-acting daily injections (42%)^[94]. In a retrospective study, 10 out of 45 patients who received LVAD implantations (37 Heartware devices and 8 Heartmate II) reported GI bleeding episodes. Endoscopy showed predominant upper GI lesions 87% and primarily AVMs. Eight patients reported rebleeding after cessation of anticoagulant medications and were prescribed octreotide. All patients reported bleeding cessation and the ability to continue anticoagulation and antiplatelet medications safely^[95]. In another multicenter retrospective analysis, 51 patients with LVAD implants who have had a history of GI bleeding events received octreotide secondary prophylaxis. They were evaluated for six years to assess bleeders vs. non-bleeders, possible risk factors, and effective management. Percentage of 76 reported no bleeding after receiving octreotide. Bleeding events, reported in 24%, were mostly angiodysplastic lesions located in the upper GI tract and in patients with a previous history of GI bleeding (33%). These patients were also compared with matched controls who had never received octreotide in a previous study and reported having significantly lower bleeding rates compared to controls (24% vs 43%)^[96]. The effect of using octreotide secondary prophylaxis every month for an average of 1.5 years in patients with LVAD-associated recurrent GI bleeding was also evaluated in another retrospective cohort study. GI bleeding frequency has significantly decreased after

octreotide use (0.7 *vs* 3.4) before octreotide prescription. Additionally, the length of hospital stays and rate of blood transfusions significantly improved^[97]. In a network meta-analysis of observational studies that evaluated the role of octreotide in secondary prophylaxis of GI ³⁵bleeding in patients with LVAD implants, octreotide showed a hazard ratio of 0.17 (Credible interval 0.0589-0.4100)^[98].

Due to the promising effect of initiating octreotide therapy on GI bleeding in patients with LVAD implantation, a clinical trial phase 1 started to assess the prophylactic effect of octreotide in patients undergoing LVAD implantation. Patients with LVAD implants within 30 d started receiving Octreotide LAR monthly for four mo. No GI bleeding events were reported in these patients after 28 wk of follow-up^[99]. This result was markedly significant as the expected GI bleeding event rate within two mo after LVAD implant is near 39%^[100].

CONCLUSION

Endoscopic treatments and surgery are widely used in treating angiodysplasia by ablation, clips, band ligation, or sclerotherapy injections. However, the outcomes of using octreotide therapy in treating GI angiodysplasia are auspicious. Octreotide induces vasoconstriction and platelet aggregation and suppresses angiogenesis leading to limited bleeding events. Adjuvant octreotide use has been associated with improved hemoglobin levels, decreased hospitalization rates, and overall lower mortality rates, as reported by various types of studies and meta-analyses.

Widespread venous malformations due to TIE2 gene mutation in BRBNS cause chronic recurrent bleeding and iron deficiency anemia. Octreotide causes decreased venous flow, pepsin secretion, and acid production, stabilizing the bleeding venous blebs and stopping clot formation. Using octreotide medical therapy can be helpful in non-operable bleeding sites, as reported in some case reports, but more clinical trials are necessary to confirm this effect.

TGF- β pathway gene mutations in HHT lead to dysregulated vascular remodeling and disrupted endothelial lining, resulting in numerous telangiectatic lesions, AVMs,

and fistulas. In severe cases, Patients may require endoscopic interventions and blood transfusion. After significant bleeding episodes, using Octreotide in HHT treatment was reported to massively reduce the number of needed endoscopic procedures and transfusion rates in different clinical trials and case reports.

Ectopic varices cause recurrent GI bleeding in patients with liver diseases, vascular thrombosis, or a history of abdominal surgery. Endoscopic procedures can be used to control the bleeding episodes. However, the effectiveness of medical therapies such as octreotide has been discussed in various case reports. Octreotide use has been associated with preventing recurrent bleeding in small bowel varices. In acute variceal bleeding, using continuous octreotide infusion has resulted in bleeding control and limited secondary episodes. Portal hypertension-associated variceal bleeding has improved after initiating octreotide, and the blood transfusion rate has markedly declined. In non-surgical cases, octreotide therapy can aid in ectopic varices treatment and decrease bleeding events. However, additional more robust studies are needed to confirm its safety and efficacy in this set of patients.

LVAD Implantation causes dysregulated angiogenesis, acquired vWF deficiency, and low pulse pressure, leading to homeostasis disruption and recurrent small GI bleeding. Multiple approaches have been used to control LVAD-associated GI bleeding, such as decreasing the anticoagulation medication dose, vWF infusion, or endoscopic interventions. Octreotide inhibits the release of angiogenesis mediators leading to decreased vascular malformations. Using octreotide in this set of patients was shown to improve blood transfusion rates, hemoglobin levels, hospital length of stay, and mortality rates. Octreotide prophylaxis after LVAD implantation was also associated with significant GI bleeding prevention.

Octreotide remains an alternative and off-label treatment in the treatment of small bowel bleeding. Additional well-conducted randomized controlled trials with larger number of enrolled patients and longer follow-up are needed to confirm the safety, efficacy, and ⁷ cost-effectiveness of octreotide in the treatment of small bowel bleeding

and whether it should be a first-line long-term treatment, emergency treatment, or a part of multi-modal management strategy.

Table 1 Summary of clinical trials assessing long-acting somatostatin analogs in treating angiodysplasia patients.

Authors	Year of publication	Number of patients	Number of transfusions before treatment	Number of transfusions after treatment	Number of transfusions	P^b	Hemoglobin levels before treatment (g/dL)	Hemoglobin levels after treatment (g/dL)	P^c	Follow-up duration
Nardone <i>et al</i> [30]	1999	17	8.8	1.5	<	0.0005	5.7	11.1	<	6 mo
Scaglione <i>et al</i> [31]	2007	13	N/A	N/A	<	0.003	13	7	<	33 mo
Bon <i>et al</i> [32]	2012	15	2	10	<	0.001	10	7	<	12 mo

Holleran 2016	24	17 patients ¹	0.35	<	9.19	11.35	<	8.8 mo
<i>et al</i> [33]		1.35		0.001				0.0027
		7 patients ¹	1.07	<				
		2.25		0.002				

^bP value for reduction of transfusions.

^cP value for reduction of hemoglobin levels.

¹{Loyaga-Rendon, 2015 #34}: 17 patients (70%) did not require blood transfusions while on treatment. However, 7 patients still required blood transfusions.

N/A: Not applicable; SD: Standard deviation.

Table 2 Summary of the observational studies demonstrating the role of octreotide in left ventricular assist device-associated gastrointestinal bleeding

Author	Year	Patients' number	Type of study	Treatment/prophylaxis	Route	Dose	Outcome
Hayes <i>et al</i> [92]	2010	5	Retrospective review	Octreotide treatment	Continuous infusion; subcutaneous injection; injection	25 µg/min; 100 µg twice daily; 10 mg each month	GI bleeding was successfully treated in all cases

Aggarwal <i>et al</i> ^[93]	2012	101	Retrospective Univariate and multivariate regression analysis	Octreotide treatment	Continuous infusion or subcutaneous injection	N/A	No difference was noticed in the length of stay, units of packed red blood cells administered, re- bleeding episodes, or mortality
Dias <i>et al</i> ^[95]	2015	8	Retrospective review	Octreotide treatment	Subcutaneous injection or intravenous infusions	100 mcg or TDS or BID	Cessation of bleeding in all cases

Smallfield <i>et al</i> ^[94]	2016	34	Retrospective cohort	Octreotide prophylaxis	secondary	Subcutaneous & (LAR) depot injections	N/A	10 cases; re-bleed
Shah <i>et al</i> ^[96]	2017	51	Retrospective analysis	Octreotide prophylaxis	secondary	38% LAR depot injection; daily subcutaneous injection	N/A	73% ± 6% freedom from; re-bleeding for 6 mo; $P = 0.7$

N/A: Not applicable; IM: Intramuscular; GI: Gastrointestinal; RBCs: Red blood cells; TDS: Three times a day; BID: Two times a day.

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