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Tranexamic acid may be a useful pharmacotherapy for endoscopically resistant small bowel angiodysplasia

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Abstract

Angiodysplasia (AD) is a benign malformation of blood vessels, and multiple ADs may occur in the small bowel. Gastrointestinal AD (GIAD) causes 10% of all GI bleeding cases and 50% of small bowel bleeding cases. When small bowel AD (SBAD) occurs frequently, it is difficult to treat all the ADs endoscopically, and GI bleeding often recurs. Pharmacotherapy is desired to reduce the bleeding in patients with SBAD who are difficult to treat endoscopically. There are a relatively large number of reports on four types of pharmacotherapies for GIAD: Somatostatin analogs, hormone therapy, thalidomide and vascular endothelial growth factor (VEGF)-neutralizing antibodies. All of these drugs have been reported to be useful, such as in reducing the amount of blood transfused, but there is no strong evidence to recommend them. Also, there are no guidelines for their use. Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disease caused by abnormalities in VEGF, resulting in multiple GIADs. A treatment guideline has been created for GIAD in HHT, and the use of tranexamic acid, an antifibrinolytic agent, is the first recommendation pharmacotherapy for GIAD with GI bleeding that is difficult to treat endoscopically. It has been reported that fibrinolysis is accelerated in GIAD patients who are not HHT, similar to HHT patients. The use of tranexamic acid for gastric antral vascular ectasia in GIAD has been studied and reported to be useful. However, there are very few reports of its use for SBAD. There are concerns with tranexamic acid use regarding the development of thrombosis/embolism due to its mechanism of action, but there are few reports of such side effects. Tranexamic acid is inexpensive and, if effective, is likely to be useful in patients with SBADs with difficult-to-control bleeding. Future clinical trials including tranexamic acid for cases of SBAD that are difficult to treat endoscopically are desired.

Key Words: Angiodysplasia; Intestine; Hereditary hemorrhagic telangiectasia; Tranexamic acid; Endoscopic treatment; Pharmacotherapy

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Core Tip: It is difficult to treat all multiple small bowel angiodysplasias (SBAD) endoscopically. Four main types of drugs, including somatostatin analogs, hormone therapy, thalidomide, and vascular endothelial growth factor-neutralizing antibodies, have been reported for use in gastrointestinal AD (GIAD). However, there is no recommended pharmacotherapy for SBAD. Tranexamic acid is recommended for patients with GIAD in hereditary hemorrhagic telangiectasia who are difficult to treat endoscopically. Investigation of the use of tranexamic acid for SBAD is desired.

INTRODUCTION

Gastrointestinal angiodysplasia (GIAD) is a benign vascular malformation of the GI tract and is a frequent source of GI bleeding. AD has been reported under various names, such as vascularectasia, angioectasa, and angiectasia, but since all of these generally present with the same lesions, they are collectively referred to here as AD. GIAD patients include patients with isolated AD in the stomach, small bowel, and large bowel; gastric antral vascular ectasia (GAVE) secondary to cirrhosis; and Heyde's syndrome secondary to aortic stenosis. GIAD causes 10% of all GI bleeding cases and 50% of small bowel bleeding cases[1]. GIAD has also been reported to cause approximately 4%-7% of upper nonvariceal bleeding, 30%-40% of occult small bowel bleeding, and 3%-40% of colonic bleeding episodes[2].

GIAD diagnosed as a source of GI bleeding often causes rebleeding even after endoscopic treatment, and subsequent treatment is difficult in these cases. After hospitalization and treatment in patients diagnosed with GIAD as the source of GI bleeding, the rate of rebleeding reaches 20% 30 d after discharge, and medical expenses are high[3]. In addition, a systematic review showed that 42.7% (209/490) of small bowel AD (SBAD) patients had rebleeding even after endoscopic treatment, and subsequent treatment is difficult in cases of rebleeding[4].

A major reason for rebleeding is that ADs tend to occur frequently. Even gastric ADs such as GAVE occur so frequently that endoscopic treatment is difficult. In addition, it has been reported that 2 or more ADs in the small bowel were observed in more than 63% of patients[5]. It is difficult to perform enteroscopy frequently for multiple SBADs, and it is difficult to find all the ADs in the long length of the small bowel. In other words, even if one lesion is treated, the other lesions bleed. Some types of pharmacotherapies are desirable for patients with SBAD whose overt bleeding or anemia progresses even after multiple endoscopic treatments. There are no established pharmacological treatments for SBAD. However, several pharmacological treatments for GIAD have been proposed, such as somatostatin analogs, hormone therapy, thalidomide and angiogenesis inhibitors.

Hereditary hemorrhagic telangiectasia (HHT) is a congenital disease in which AD occurs frequently in various organs. In HHT, GIADs occur so frequently that endoscopic treatment is difficult. Therefore, the pharmacotherapy of HHT has been studied for a long time, many reports have been published, and guidelines have been established. In this paper, the GI bleeding section of the HHT guideline is outlined, the pharmacotherapy options for GIAD that have been performed thus far are introduced, and finally, the treatment policy for SBAD is considered based on the HHT guideline.

GUIDELINE FOR HHT

HHT is a multiorgan disease in which AD occurs frequently in the skin, mucous membranes, and GI tract, causing recurrent bleeding and arteriovenous malformations (AVMs) in the brain, spinal cord, lungs, and liver[6,7]. HHT is inherited in an autosomal dominant manner and is caused by abnormalities in vascular endothelial growth factor (VEGF)[8]. The gene associated with HHT type 1 is a transforming growth factor-beta binding protein of endothelial cells[9]. HHT types 1 and 2 arise from mutations in endoglin and activin receptor-like kinase 1, respectively[10].

Epistaxis is a serious problem in HHT patients, but GI bleeding due to multiple GIADs is also a major problem. HHT has international guidelines, updated in 2020[11].

The guidelines recommend endoscopic treatment for GIAD in patients with HHT first. Second, antifibrinolytic therapy is encouraged as pharmacotherapy for endoscopic treatment resistant cases. However, the degree of encouragement is weak. This guideline is due to a recent report that showed that the antifibrinolytic agent tranexamic acid reduced the need for endoscopic management in patients with HHT[12]. The latest report summarizing the main points of the guideline recommends using tranexamic acid as the first step after performing argon plasma coagulation of actively bleeding lesions at the initial diagnosis. Systemic antiangiogenic agents are recommended as a next step if no improvement is seen with administration of tranexamic acid[13]. The guideline committee states that, where possible, the use of dual antiplatelet therapy and/or a combination of antiplatelet therapy and anticoagulation should be avoided in patients with HHT. If anticoagulation is not tolerated in HHT patients with atrial fibrillation, discontinuation of anticoagulation with alternative approaches, such as left atrial appendage closure, is recommended[14]. Since the bleeding in HHT patients tends to be serious, the use of anticoagulant therapy and antiplatelet therapy is recommended with the minimum amount that is necessary.

Patients with multiple SBADs often have fewer ADs than patients with HHT. However, SBAD is a similar pathology, and HHT is a reference for SBAD treatment. There are no trials of tranexamic acid in the pharmacological treatment of SBAD in non-HHT patients, nor does tranexamic acid appear in various reviews as a treatment for SBAD. The next section considers the drug treatment of GIAD, especially SBAD, with reference to HHT.

PHARMACOLOGICAL TREATMENT OF GIAD

According to an analysis of the MEDLINE, Cochrane, Scopus and Embase databases, there are four main pharmacological therapies for GIAD that have been reported: somatostatin analogs, hormone therapy, thalidomide and angiogenesis inhibitors[15]. These drugs are discussed first, followed by a discussion of tranexamic acid, which is used in the treatment of HHT.

Hormone therapy

Studies of oral contraceptives have shown that there is a risk of thrombosis with hormonal therapy with estrogens and progestogens[16]. It has been reported that this hormone therapy affects blood clotting ability and shortens bleeding time[17], which leads to its use as a hemostatic agent. Activated protein C resistance was reported to be involved in this coagulation enhancement[18]. On the other hand, postmenopausal hormonal therapy has been reported to increase plasma fibrinolytic activity, plasma levels of D-dimer and tissue plasminogen activator activity[19]. Thus, the therapy does not appear to increase coagulability in postmenopausal women. The increase in plasma fibrinolytic activity due to postmenopausal hormone therapy may be considered a secondary phenomenon of hypercoagulability. Fundamentally, hormone therapy for GIAD is considered to be an attempt to utilize the enhancement of blood coagulability for hemostasis against GI bleeding.

In a double-blind, placebo-controlled, crossover trial using estrogens and progestogens in 10 patients with GIAD requiring frequent blood transfusions, it was reported that hormone therapy reduced the amount of transfusion[20]. Various studies have originated from this Lancet report in 1990. In a prospective observational study with an average follow-up period of 535 d in 43 patients with obscure GI bleeding, all 38 who received concomitant hormonal therapy were bleeding-free. In contrast, all 5 patients treated with estrogen alone had episodes of rebleeding[21]. However, a double-blind randomized control trial (RCT) was conducted in 72 noncirrhotic patients with hemorrhages of GIAD-probable origin; rebleeding occurred in 46% of the 35 patients; and no significant difference was observed[22]. As a result of this study, the number of reports on hormone therapy has decreased, but reports on treatment using hormone therapy have been published recently. For example, when comparing 6 mo before and after hormone therapy for GIAD, anemia improved, and the number of blood transfusions decreased[23].

Hormone therapy has side effects peculiar to hormone drugs, but it is generally safe and has the advantage of being inexpensive. For these reasons, the search for a hormone therapy treatment for difficult-to-control GI bleeding continues.

Somatostatin analogs

Since the 1990s, attempts have been made to use the somatostatin analogs octreotide and lanreotide to treat hemorrhagic GIAD. Somatostatin analogs for GIAD are thought to inhibit angiogenic promoters by affecting chemical factors such as VEGF, basic fibroblast growth factor, and insulin-like growth factor 1 and to stimulate relaxation of intestinal smooth muscle, relieve chronic submucosal vein occlusion, and reduce the intravascular pressure on the arterial side[24]. There are many reports showing that somatostatin analogs are effective in patients with GIAD, but most have a small number of patients and are retrospective studies[1]. The usefulness of somatostatin analogs was reported in an RCT targeting 70 patients in which the actuarial probability of remaining free of rebleeding at 1 and 2 years of follow-up was 77% and 68%, respectively, in the octreotide group and 55% and 36%, respectively, in the placebo group ($P = 0.030$)[25].

Recently, a systematic review of 212 patients from 11 studies investigating the usefulness of somatostatin analogs for patients with GIAD, with a median duration of treatment of 12 mo, was reported. Somatostatin analogs were reported to reduce the number of red blood cell transfusions by an incidence rate ratio of 0.18 ($P < 0.0001$). The most common side effects of somatostatin reported in this study were loose stools (3%), cholelithiasis (2%), flatulence (2%), and administration site erythema (2%)[26]. Another systematic review and meta-analysis suggested that somatostatin analogs are more useful in patients with GIAD than hormone therapy[27].

Based on the above, somatostatin analogs are thought to be useful for the treatment of patients with GIAD. However, since most somatostatin analogs are a daily subcutaneous injection and are expensive, there is a high possibility that the number of patients that can be treated with them are small.

Thalidomide

Thalidomide was reported to inhibit angiogenesis by suppressing VEGF[28]. Recently, it was reported that EGF-like domain multiple 6 (EGFL6) is overexpressed in patients with SBAD, and *in vitro* and *in vivo* assays reveal that thalidomide can act as an anti-angiogenic agent through the regulation of EGFL6 in a proteasome-dependent manner[29].

One RCT showing the efficacy of thalidomide for patients with GIAD has been published. The study randomized 55 patients with GIAD to receive either thalidomide 100 mg (n = 28) or iron 400 mg (n = 27, controls) daily for 4 mo. The treatment was considered to be effective when patients showed a 50% or greater reduction in bleeding episodes (fecal occult blood) in the first year of follow-up; the response rates in the thalidomide group and the control group were 71.4% and 3.7%, respectively ($P < 0.001$)[30].

Thalidomide is also considered useful in patients with HHT[31]. However, it is not explicitly mentioned in the HHT guidelines and is considered to be included among other systemic antiangiogenic therapies[11]. Thalidomide is highly teratogenic, and since it was developed as a sleeping drug, it has been shown to cause neurological symptoms such as somnolence in a drug-dependent manner. These issues limit its use.

VEGF-neutralizing antibodies

As previously mentioned, HHT is caused by abnormalities in VEGF. First, a VEGF-neutralizing antibody was reported to prevent cutaneous AVM formation and ameliorate the internal bleeding in Alk1-deficient adult HHT model mice[32]. In animal experiments, sorafenib and a pazopanib analog were reported to be effective against a mouse model of HHT, and there have been many case reports of the effectiveness of bevacizumab for HHT[33-39]. However, since these are all case reports, generally, VEGF-neutralizing antibodies cannot be judged to be effective, and further investigation is needed.

On the other hand, patients with GIAD did not show any abnormalities in their VEGF levels. In patients with GIAD, angiopoietin-2 was increased, but VEGF did not increase[40]. Similarly, when the serum from patients with SBAD, portal hypertensive gastropathy, and GAVE was compared with the serum from nonbleeding, nonanemic control patients, angiopoietin-2 was increased, but there was no difference in the blood VEGF concentration[41]. Although the relationship between GIAD and VEGF is not clear, there are reports that VEGF-neutralizing antibodies are effective in patients with GIAD. A study reported that bevacizumab was effective for treating GIAD in two patients with Heyde's syndrome[42]. There is one case report involving Heyde's syndrome[43] and another case report showing that bevacizumab is useful for patients with GIAD[44].

Since the number of reports is still small, VEGF-neutralizing antibodies cannot be judged to be effective, and further examination is necessary. Even if effective, VEGF-neutralizing antibody preparations are extremely expensive and difficult to use in many patients.

Tranexamic acid

Plasma hyperfibrinolysis has been reported to occur in both patients with HHT[45] and patients with hemorrhagic GIAD[46]. The latter report suggests that intrinsic ischemia may be the cause of GIAD, which may result in increased fibrinolytic activity in patients with GIAD. This plasma hyperfibrinolysis may promote GI bleeding in patients with GIAD. Tranexamic acid has been widely used as a hemostatic agent for many bleeding disorders by utilizing its anti-hyperfibrinolysis action. Tranexamic acid is a synthetic derivative of the amino acid lysine and exerts antifibrinolytic effects through reversible blockade of the lysine binding site on the plasminogen molecule[47].

A comparative study published in 1973 showed that tranexamic acid is effective in stopping bleeding in the upper GI tract[48]. Gastric juice has been reported to induce marked fibrinolysis, and tranexamic acid was expected to stop bleeding, especially in gastric lesions[49]. In a meta-analysis, tranexamic acid was shown to reduce mortality in

patients with upper GI bleeding by 5%-54% and by 40% compared to placebo and is expected to be effective in a variety of nongastrointestinal bleeding disorders[47]. Tranexamic acid was also used for GAVE in patients with cirrhosis that was unresponsive to propranolol therapy and transjugular intrahepatic portosystemic shunt and was reported to reduce bleeding by 20%-30% and the need for surgery by 30%-40%[50-52].

As mentioned above, although the recommendations for it are weak, tranexamic acid is considered to be the first-choice drug for GI bleeding in patients with HHT that is difficult to treat endoscopically. For GIAD, it was reported for the first time in 1998 that tranexamic acid is effective for treating chronic bleeding from colonic AD in dialysis patients[53]. Jejunal AD with persistent bleeding is called Bernard-Soulier, and it was reported in 2013 that tranexamic acid is an effective treatment[54]. Tranexamic acid was reported to be very effective in a patient with multiple duodenal and jejunal ADs who had a medical history of ineffective hormone therapy; discontinued thalidomide treatment due to side effects such as nausea, dizziness, and severe fatigue; and discontinued octreotide treatment after one dose due to a hypoglycemic episode[55]. However, there are still only a few reports of the use of tranexamic acid for patients with SBAD.

Since tranexamic acid is an antifibrinolytic agent, there are concerns about thrombosis and embolism, and the following reports have been published. First, there are reports of ischemic episodes and pulmonary embolisms with the use of tranexamic acid[52]. In addition, there is a case report in which tranexamic acid was used to treat SBAD in dialysis patients for whom endoscopic treatment was difficult, and thrombosis of the arteriovenous fistula occurred[56]. In contrast, a meta-analysis of 4747 patients undergoing cesarean section or vaginal delivery found no association between tranexamic acid and deep vein thrombosis[57]. Additionally, in an RCT conducted in patients undergoing bilateral total knee arthroplasty, adverse effects such as deep vein thrombosis and pulmonary embolism were not significantly different between 245 patients who received tranexamic acid and 271 who did not[58]. Furthermore, a review

of short-term tranexamic acid use in postdental surgery patients on anticoagulant therapy found no complications, such as thrombosis, in 125 tranexamic acid-treated patients[59]. Based on these reports, tranexamic acid appears to be relatively safe for short-term use. However, there have been no reports on the long-term use of tranexamic acid, especially during anticoagulant or antiplatelet therapy for myocardial infarction or cerebral infarction, and caution should be exercised when using tranexamic acid in patients with these high-risk diseases. Although there are concerns about the risks described above, tranexamic acid is an inexpensive drug that can be expected to reduce the amount of GI bleeding in patients with SBAD who are difficult to treat by endoscopy. Future reports are needed.

CONCLUSION

Table 1 summarizes the drugs currently being studied for use in patients with GIAD, including SBAD. There are several reports that hormone therapy, somatostatin analogs, thalidomide and VEGF-neutralizing antibodies are useful for SBAD for which endoscopic treatment is difficult. Hormone therapy is a good choice considering its less side effects and costs, but there are negative reports. Due to the small number of reports, it is not possible to decide which drug to strongly recommend. Tranexamic acid has been adopted as a first-line pharmacological treatment in the guidelines for GIAD in HHT patients who are difficult to treat endoscopically. It is also effective for GAVE in non-HHT patients. Although there are concerns about the risk of thrombosis and embolism, tranexamic acid is expected to reduce the amount of GI bleeding in patients with SBAD in whom endoscopic treatment is difficult. Future reports are expected, as tranexamic acid could be a first-line drug for patients with SBAD.

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