Oral Drug for Small Intestinal Angiodysplasia Bleeding: Every Cloud Has a Silver Lining!!

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Abstract

Because of both difficulties in accurate diagnosis and appropriate management, small bowel bleeding due to angiodysplasia remains a challenging and perplexing issue in clinical practice. Advancement in small bowel endoscopy including capsule endoscopy as well as balloon enteroscopy has expanded the domain of endoscopic hemostatic interventions in the small bowel. This has led on to marked improvement in immediate homeostasis rates in patients with small bowel angiodysplasias (SBA) bleeding. However, high recurrent bleeding rates are an important limitation of endoscopic interventions. Therefore, there is an unmet need of an effective therapeutic as well as prophylactic pharmacotherapy that can alter the course of the disease. Long-acting octreotide as well as thalidomide has been used in patients with SBA bleeding with encouraging results, but the evidence on their efficacy is not robust. In news and views of this issue, we discuss a randomized controlled study that investigates the efficacy and safety of thalidomide for the treatment of recurrent bleeding due to SBA.

Keywords
- capsule endoscopy
- enteroscopy
- angiodysplasia
- octreotide
- thalidomide

Small intestinal bleeding remains a challenging and perplexing issue in clinical practice.[1–3] Various international societies have tried to address this entity to varying extent. American College of Gastroenterology (ACG) replaced the term obscure gastrointestinal (GI) bleeding with small intestinal bleeding because of the refinement and improvement in the technology of direct endoscopic visualization of small bowel mucosa by capsule video endoscopy.[4] European Society of Gastrointestinal Endoscopy (ESGE) guidelines have endorsed video capsule endoscopy as the first-line modality for diagnosis of small bowel bleeding.[5] Of the various causes of obscure GI bleeding, small bowel angiodysplasias (SBA) remains an important cause contributing to 5 to 10% of these episodes.[2,6–8] Small bowel bleeding can manifest as overt bleeding, either as melena or hematochezia or it can be in form of occult bleeding manifesting as iron deficiency or it can be detected in stool sample as occult blood positivity.[6] Angiodysplasias are ectatic vessels that form in the mucosa and submucosa and these aberrant vessels are prone to bleeding. These vascular lesions tend to cause rebleeding in a majority of cases and cause significant morbidity.[1,6,7,9]

There have been various trials that have looked at the management of GI bleeding due to SBAs. Different therapeutic measures that can be used include medical therapies, endoscopic management, radiological embolization, and surgical therapies. Endoscopic therapy entails the usage of mechanical therapy like hemostatic clips or ablative form of therapy using argon plasma coagulation. In a systematic review of utility of endoscopic therapy versus expectant management, it was shown that the rates of rebleeding were 42.7% (95% confidence interval [CI]: 38–47%) in endoscopy arm versus 49.2% (95% CI: 40–58%), in the expectant arm, thereby suggesting that endoscopic therapy is ineffective in bleeding from SBAs.[10] Another meta-analysis showed similar results with rebleeding rates of 45% with endoscopic therapies in patients with SBA bleeding.[11] Similarly, interventional radiology-guided super selective embolization results in high immediate hemostasis rates but is associated

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with high rebleeding rates up to 22%.[12] These high recurrent bleeding rates are due to multisite nature of the disease resulting in lesions in areas that are nonaccessible or nonlocalizable. Because of this reason, pharmacotherapy may be more effective management option for durable response.

Several drugs have also been tried for the management of small intestinal bleeding. Initially, hormonal therapies were tried with mixed results, but hormonal manipulation had multiple undesired side effects and the enthusiasm for its use gradually dwindled.[13] Somatostatin analogues have also been evaluated in small bowel bleeding with encouraging results. These agents tend to cause splanchnic vasoconstriction and limit the production of vascular endothelial growth factor (VEGF).[2] In a retrospective study, long-acting analogue of octreotide was used in 98 patients with angiodysplasia and authors reported significantly better control of bleeding with 40.8% having complete control of bleeding, 32.6% having a relapse of bleeding episode, and 26.5% patients not responding.[14] A nonrandomized comparative study comparing 32 refractory SBA bleeding patients treated with octreotide to an external placebo control group of 38 patients reported a significant decrease in rebleeding rate and need for oral iron.[15] Recently, bevacizumab, VEGF inhibitor, has also been shown to be effective treatment option for SBA bleeding as evident by marked reduction in the rate of blood transfusions, intravenous iron infusions, and endoscopic interventions.[16]

Both octreotide and its analogues as well as bevacizumab need to be administered parenterally and there is a need of an oral effective drug for SBA bleeding. Various case reports and small case series have suggested efficacy of thalidomide in the prevention of bleeding in SBAs.[17–20] An open-label randomized controlled trial of 55 patients who were either given 100 mg thalidomide ($n = 28$) or 400 mg iron ($n = 27$, controls), daily for 4 months reported that proportion of patients in whom bleeding episodes had decreased by more than or equal to 50% in the first year of the follow-up period was significantly higher in the thalidomide group (71.4 and 3.7%, respectively; $p < 0.001$).[21] Also, the rates of cessation of bleeding, blood transfusion, overall hospitalization, and hospitalization for bleeding were significantly lower in the thalidomide group with no serious adverse effects. The same group conducted a multicenter, double-blind, randomized, placebo-controlled trial to investigate the efficacy and safety of thalidomide for the treatment of recurrent bleeding due to SBA.[22]

The authors enrolled patients with recurrent bleeding (at least four episodes of bleeding during the previous year) due to SBA and randomly assigned them to receive thalidomide at an oral daily dose of 100 mg ($n = 51$) or 50 mg ($n = 49$) or placebo ($n = 50$) for 4 months. These enrolled patients were given thalidomide for 4 months and thereafter followed for at least 1 year. Reduction by at least 50% in the number of bleeding episodes that occurred during the year after the end of treatment compared with the episodes that occurred during the preceding year before treatment was defined as effective response. The other outcome measures assessed were cessation of bleeding without rebleeding, blood transfusion, hospitalization because of bleeding, duration of bleeding, and hemoglobin levels.

The primary end-point differed significantly across the three groups: 68.6% in the 100-mg thalidomide group, 51.0% in the 50-mg thalidomide group, and 16.0% in the placebo group ($p < 0.00$). Also, during the 4-month treatment period, the incidence of rebleeding was 27.5% in the 100-mg thalidomide group, 42.9% in the 50-mg thalidomide group, and 90.0% in the placebo group. Seventeen percent patients in the 100-mg thalidomide group, 24.5% in the 50-mg thalidomide group, and 62.0% in the placebo group received blood transfusion during the first follow-up period. Side effects were observed in 68.6% of the patients in the 100-mg thalidomide group, 55.1% of the patients in the 50-mg thalidomide group, and 28.0% of the patients in the placebo group with constipation being the most common adverse event. Also, somnolence, peripheral edema, elevated liver-enzyme levels, and dizziness were more common in the thalidomide groups than in the placebo group. All the side effects were grade 1 or 2 and resolved after treatment of symptoms, after completion of treatment period, or after discontinuation of drugs and no serious adverse events were reported. The authors concluded that thalidomide resulted in a significant reduction in bleeding episodes during the year after the 4-month treatment period in patients with recurrent bleeding due to SBA.

Commentary

With advancement of techniques, small intestinal source of bleeding is being detected more often than not and obscure GI bleeding is restricted to cases with normal upper, lower GI endoscopy, and small bowel capsule endoscopy/enteroscopy and normal radiological imaging.[2] Medical therapies seem to be paramount in the management of such cases as rebleeding is a common occurrence after minimally invasive hemostatic techniques involving both endoscopy and interventional radiology.[10–12] Moreover, the expertise of performing them may not be available at all the centers and, therefore, putting medical therapies at the helm of affairs. Long-acting release formation of octreotide has been in use for with good results.[2,14,15] However, cost as well as need for parenteral administration is important limitation. Thalidomide has shown promising results but the evidence has not been robust. Also, adverse effects including neurotoxicity, venous thrombosis, and the risk of teratogenicity are considerations that limit its use.[23–25] The randomized study discussed in the these news and views has provided a high-quality evidence of efficacy of thalidomide in SBAs bleeding. Also, this study shows that hemostatic efficacy persists after discontinuation of the drug suggesting that thalidomide may be a disease-modifying drug for SBAs. Moreover, the low cost along with oral administration is other advantage of thalidomide. Despite this randomized study proving the efficacy of thalidomide in management of SBAs bleeding, few questions remain unanswered:

1. The duration of treatment and need, if any, of repeating the course of thalidomide is unclear.

2. The efficacious and safe dose of thalidomide is not clear as both 50 and 100 mg daily dose was used in this study with 100 mg dose being more efficacious than 50 mg but with higher incidence of adverse effects. It appears that a better strategy will be to start with an initial dose of 50 mg daily followed by increase to 100 mg depending upon clinical response and adverse effects.

Despite these limitations, the clinicians now have a choice of costly long-acting octreotide that may have better compliance of single injection once a month with minimal adverse effects and cheaper thalidomide that can be taken orally but have higher incidence of adverse effects. A comparative randomized study between thalidomide and octreotide can only decide the best drug for SBA bleeding and till that time the choice can be based upon economics, compliance, and risk of adverse effects. Thalidomide may indeed be a silver lining in the dark clouds of SBA bleeding!

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Conflicts of Interest
None declared

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