

# Provocation of Bleeding During Endoscopy in Patients With Recurrent Acute Lower Gastrointestinal Bleeding

Atul Kumar, MD<sup>1,2</sup>  
 Frederick Gandolfo<sup>1</sup>  
 Bhawna Halwan, MD<sup>1</sup>

<sup>1</sup>State University of New York at Stony Brook; <sup>2</sup>Northport VA Medical Center, Northport, NY

**M**anagement of recurrent acute lower gastrointestinal bleeding (GIB) is problematic, as the bleeding is intermittent and often ceases by the time of diagnostic or therapeutic intervention. If a bleeding site can be identified, endoscopic therapy is a safe and effective intervention that may affect outcomes.<sup>1,2</sup>

Heparin administered during endoscopy for hemostasis has been reported in two case reports as provocation of bleeding.<sup>3,4</sup> In one report, the administration of 10,000 U of heparin followed by an infusion of 1,000 units/hr resulted in active bleeding within 90 minutes in a vascular malformation near an ileostomy site.<sup>4</sup> In another case report, 5,000 U of heparin administered intravenously caused active bleeding within 2 hours in a Dieulafoy lesion in the stomach.<sup>3</sup>

## Case Report

A 65-year-old man with two prior episodes of left-sided diverticular bleeding was admitted with profuse hematochezia. Upper endoscopy performed within 12 hours was unremarkable, and colonoscopy was incomplete due to excessive looping. Tagged red-cell scintigraphy localized the bleeding site to the distal small bowel, whereas angiography localized the bleeding to the hepatic flexure. Bleeding spontaneously ceased but recurred approximately two days later and when colonoscopy was repeated. Intravenous heparin of 10,000 U was administered, and the colon and terminal ileum were re-examined over a 75-minute period; however, no source of bleeding could be identified. Twelve hours after colonoscopy, the patient began rebleeding and was taken to surgery, where a distal ileal carcinoid was found as the source of the bleeding.

## Discussion

Management of patients with GIB of obscure source who continue to bleed intermittently is problematic. Angiography may be therapeutic but is associated with complications such as gut ischemia and perforation.<sup>5,6</sup> Tagged

red-cell scintigraphy and angiography are often unreliable, as in this case, and can lead to therapeutic misadventure. Among patients with active bleeding, colonoscopy can reliably identify the site and direct definitive therapy.<sup>7</sup>

Surgery should be a means of last resort, as it is associated with significant morbidity and mortality.<sup>8,9</sup> Although our attempt was unsuccessful, this strategy should be considered among patients with recurrent and profuse GIB, especially in poor surgical candidates.

Provocative testing should not be avoided for fear of causing uncontrollable hemorrhage, as the anticoagulative effects of heparin are short-lived and are easily reversible with protamine. However, the optimal dosage for anticoagulation with heparin is not known and most likely has to be individualized. It is also likely that a higher dose of heparin may be required to provoke bleeding among patients with lower GIB, as the size of the bleeding vessel is smaller than that in upper GIB lesions. Although provocative testing during endoscopy may be labor-intensive and time-consuming, further clinical trials may be conducted to help outline its role for acute obscure GIB in patients who may be poor surgical candidates.

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Address correspondence to:

Dr. Atul Kumar, Northport VA Medical Center, 79 Middleville Road, Northport, NY 11790; E-mail: akumar1165@yahoo.com

## Review

### Recurrent Obscure Gastrointestinal Bleeding: Time for Provocative Thinking?

Steven B. Ingle, MD, and Jeffrey A. Alexander, MD

*Miles and Shirley Fiterman Center for Digestive Diseases,  
Mayo Clinic College of Medicine, Rochester, Minn.*

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unclear origin after a complete evaluation by standard endoscopic techniques, usually esophagogastroduodenoscopy (EGD) and ileocolonoscopy. Among the more than 300,000 patients hospitalized annually for gastrointestinal bleeding (GIB), approximately 5% have recurrent OGIB.<sup>1</sup> After initial evaluation, a repeat lower endoscopy has a yield of 5–10% and is performed on a selective basis. Push enteroscopy is routinely performed in the evaluation of OGIB and has a yield of over 30%.<sup>2</sup> Although many lesions are located within reach of standard upper endoscopes, push enteroscopy has been shown to be a more cost-effective approach than EGD in patients with iron deficiency anemia and OGIB.<sup>3</sup>

If bleeding is active and no source has been identified, a nuclear medicine bleeding scan can be performed. If the scan confirms active bleeding, an immediate angiogram can reveal the source of bleeding in approximately two-thirds of cases.<sup>4</sup> If the bleeding is slow or inactive and no bleeding source has been identified by push enteroscopy, capsule endoscopy (CE) has a diagnostic yield of 70% and results in an alteration of clinical management in approximately half of all cases.<sup>5–7</sup> Double-balloon enteroscopy (DBE) appears to be a promising option for OGIB<sup>8–10</sup> and has a complementary role to CE,<sup>11,12</sup> even though DBE is labor-intensive. Novel radiologic imaging modalities may also prove useful. In a preliminary investigation, we found triphasic computed tomography (CT) enterography to be complementary to CE, with the advantage of more accurate localization of bleeding compared with CE alone.<sup>13</sup>

In an attempt to increase diagnostic yield and hasten therapeutic intervention, provocation of bleeding using anticoagulants or thrombolytics has been reported in several case reports and small case series.<sup>14–24</sup> The majority of these cases involve provocative angiography, in which

systemic or intra-arterial heparin, urokinase, streptokinase, or a vasodilator, either alone or in combination, are delivered to lyse the clot at the site of the recent bleed and allow for identification of the bleeding site. Mernagh and coworkers increased the diagnostic yield of angiography two-fold from 33% to 67% using an intravenous heparin bolus (5,000 U) followed by a heparin drip.<sup>19</sup> Koval and associates described a stepped approach in patients with lower gastrointestinal bleeding (LGIB) and negative angiography.<sup>18</sup> Intravenous heparin (5,000–10,000 U) was administered prior to angiography, which resulted in a positive study in 2 patients (20%). The remaining 8 patients were given intra-arterial tolazoline, a potent arterial vasodilator, which resulted in a positive study in 5 patients. Streptokinase was selectively infused into the superior mesenteric artery of the remaining 2 patients, resulting in a positive study in 1 patient. In total, the diagnostic yield increased from 32% to 65% using provocative measures. However, two major complications, puncture site hematoma and postprocedural bleeding, occurred in this study.

Other studies have also examined the use of anticoagulants to increase diagnostic yield. Malden and colleagues reported less striking results using intravenous heparin and urokinase, and identified a source in 40% of the cases, which led to treatment in 20% of cases, although the investigators selected patients who had no clinical evidence of bleeding within two days of the study.<sup>24</sup> Bloomfeld and coworkers also reported a lower diagnostic yield of 29% in a review of 7 patients undergoing provocative angiography with intravenous heparin, tolazoline, and/or urokinase.<sup>15</sup> None of the patients given heparin alone had their bleeding source identified, although heparin dosages varied widely and were low: 4 of 6 patients received a dose lower than 5,000 U. In another study, Ryan and associates combined intravenous heparin with intra-arterial tolazoline and tissue plasminogen activator (tPA) to induce bleeding in 16 patients with occult LGIB, and were able to identify lesions in 37.5% of patients. This technique contributed to treatment in 50% of patients, and no significant complications were reported.<sup>22</sup> Although this strategy appears effective, optimal agent selection and dosing remain unclear. Given the wide disparity in outcomes and study design, head-to-head comparisons are difficult, and provocative angiography has yet to be accepted as the standard of care in most institutions.

If provocative angiography holds promise for identifying bleeding lesions in patients with OGIB, it stands to reason that provocative endoscopy may also be effective without the accompanying risks of angiography. There are no associated case series in the published literature; however, there have been several case reports on provocative endoscopy. In their case report, Kumar and colleagues

Address correspondence to:

Dr. Jeffrey A. Alexander, Mayo Clinic GI 19E, Mayo Clinic, 100 First Street SW, Rochester, MN 55905; Tel: 507-538-0474.

describe the administration of an intravenous bolus of 10,000 U heparin prior to ileocolonoscopy in an unsuccessful attempt to increase the diagnostic yield in a patient with obscure LGIB.<sup>25</sup>

Although Kumar and colleagues were ultimately unsuccessful, others have reported positive results using similar strategies. For example, Berkelhammer and associates identified a small-bowel Dieulafoy-like lesion in a patient with refractory bleeding after the intravenous administration of 10,000 U heparin followed by a continuous 1,000 U/hour bolus.<sup>26</sup> This patient had previously undergone provocative angiography with heparin, urokinase, and tolazoline, which failed to reveal the bleeding source. In an earlier study with our colleagues, we reported a gastric Dieulafoy lesion found with standard upper endoscopy only after the intravenous administration of 5,000 U of heparin in a patient who had undergone angiography, red-cell scintigraphy, and two upper endoscopies.<sup>27</sup> Rieder and colleagues also recently reported a case of provocative bleeding during CE in a patient with recurrent melena and iron deficiency anemia whose bleeding source remained unclear after endoscopy, push enteroscopy, magnetic resonance enteroclysis, and standard CE.<sup>28</sup> After the administration of intravenous heparin for a period of 12 hours, repeat CE revealed several bleeding sites in the proximal jejunum. At laparotomy, a gastrointestinal stromal tumor was found in the patient. It is important to note that none of these patients experienced bleeding complications related to the administration of heparin. As with provocative angiography, agent selection and dosing remain unclear. In patients with more subtle GIB, heparin bolus followed by a continuous drip might increase diagnostic yield. Urokinase, streptokinase, and tPA have not been studied in this arena. Further study is needed to establish both efficacy and safety.

An additional agent of interest is naloxone, an opiate antagonist, which can be administered to reverse the effects of meperidine during colonoscopy. Meperidine causes hypotension and decreased peripheral resistance that may make bleeding lesions more difficult to identify. Brandt and coworkers studied 0.4–0.8 mg of naloxone given intravenously in patients 60 years and older undergoing colonoscopy, and found vascular ectasias in 4 patients (2.7%), which had not been visualized by standard endoscopy. The investigators also found that naloxone increased the size and number of ectasias in a number of patients.<sup>29</sup> Although most patients in this study were not bleeding, using naloxone might be a reasonable approach in elderly patients with obscure LGIB undergoing endoscopy.

Many patients with OGIB are on long-term oral anticoagulants. Performing endoscopic procedures with warfarin has been suggested as a cost-effective approach.<sup>30</sup>

However, no data reported to date have shown the potential increased yield of evaluation on anticoagulation. Although not an approach we traditionally use in clinical practice, endoscopic therapy at modest levels of anticoagulation does appear to be safe.<sup>31,32</sup>

Fortunately, most cases of gastrointestinal bleeding are readily identified and treated with standard endoscopy. Nonetheless, OGIB remains a common problem encountered by gastroenterologists. Technological advances in endoscopy, angiography, and radiography have altered the landscape and will continue to do so in the future. As CE and DBE become widely available, these complementary modalities will likely increase diagnostic yield significantly. CT enterography is noninvasive and will complement both routine and advanced endoscopic procedures. Although the role of provocative endoscopy remains unclear, it may be appropriate in patients with recurrent OGIB who do not have an identified bleeding source despite extensive evaluation. One might postulate that anticoagulation followed by CE, or potentially CT enterography, may be the safest and most reasonable first step in this challenging group of patients.

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