Occult gastrointestinal (GI) hemorrhage can be a great challenge to both patients and physicians, exerting a great toll on patients and the healthcare system. While diagnostic capabilities for diagnosing GI bleeding are improving, particularly with the establishment of computed tomography angiography and capsule endoscopy as routine modalities, patients with intermittent massive GI bleeding continue to pose a diagnostic and management dilemma. In this review, the concept, efficacy, and safety of provocative mesenteric angiography is described. The body of literature suggests that this procedure is safe and effective in this patient population with little to no alternative options.

Introduction

Gastrointestinal (GI) hemorrhage is a common occurrence in a variety of disease states including the setting of uncertain etiology. While surgical resection of the affected segment of GI tract has historically been considered the definitive treatment, identification of the bleeding segment is required. Advances in endoscopic and endovascular techniques have provided a spectrum of minimally invasive therapies that are currently first-line in management of GI hemorrhage. While endoscopic techniques are excellent for identification and treatment of bleeding mucosal lesions, these are limited by physical accessibility by the endoscope and presence of excessive food, stool, or blood that obscures visualization. Endovascular techniques are free from these two factors, but requires a substantial rate of bleeding in order to allow identification and treatment of hemorrhage. In cases where radiologic, endoscopic, and angiographic attempts have failed to identify the source of hemorrhage, patients and physicians are faced with a dire dilemma. These patients typically undergo numerous repeated episodes of hemorrhage, incurring multiple radiologic studies, multiple angiographic and endoscopic procedures, multiple hospitalizations, and multiple blood transfusions. Surgical resection cannot be performed without knowing the actual site of hemorrhage. Even if the site is known, many patients are poor surgical candidates. The cumulative risk with these repeated procedures is substantial and the costs incurred by these multiple hospitalizations, procedures, and studies are enormous. There is therefore a need for additional strategies for identifying and treating occult GI hemorrhage.

Diagnosing GI Bleeding

Identification of the site of GI hemorrhage is crucial for treatment regardless of the modality. With surgical resection of the affected segment of bowel as the most definitive treatment for hemorrhage, localization of the source bleeding must be previously accomplished, since laparotomy or laparoscopy allows visualization only of the adventitia of bowel. However, in cases where a bowel wall mass is the culprit, the mass may be directly visible or easily palpated if large enough, which would allow definitive resection.

Radiologic studies are highly valuable as noninvasive methods to diagnose and localize GI hemorrhage. Tagged red blood cell scintigraphy is a well-established method for detecting GI hemorrhage. This technique, conducted over the course of an hour or more, allows real-time imaging of blood that has extravasated into GI lumen. Scintigraphy is highly sensitive for detecting the presence of active GI bleeding; however, localization to the exact
loop of bowel can be challenging due to the typically planar imaging and low spatial resolution. While scintigraphy can accurately localize a segment of colon adequately to guide resection, it is rarely feasible with small bowel.

Computed tomography angiography (CTA) has emerged as a highly sensitive, specific, and accessible diagnostic modality that is increasingly becoming the first-line radiologic modality for the diagnosis of GI hemorrhage. It can be performed within minutes and does not require significant time-consuming and resource-intensive preparation as does scintigraphy. While CTA is not as sensitive as scintigraphy for the detection of subtle hemorrhage, it has the advantage of markedly superior spatial resolution, which can not only demonstrate the exact site of hemorrhage more reliably than scintigraphy, but can also identify other etiologies not demonstrable on scintigraphy, such as bowel wall masses that may guide therapy, such as resection. In fact, CTA has been shown to be more sensitive than capsule endoscopy for detecting bleeding sources and the etiology in the small bowel.

Furthermore, while the sensitivity of CTA is less than scintigraphy for detecting very slow-rate hemorrhage, this feature has been deemed an advantage in selection of patients who may benefit from angiography, since CTA has intermediate sensitivity between scintigraphy and conventional angiography in terms of minimal rate of detectable bleeding, thus leading to more positive angiograms when used for screening. Finally, CTA can detect varices, including ectopic varices, that represent a non-arterial source of GI hemorrhage.

Endoscopy has emerged as the first line modality for upper GI hemorrhage. One of the great strengths of upper endoscopy is the ability to reliably diagnose the site and etiology of upper GI bleeding, but also to frequently treat sources of hemorrhage with high technical and clinical success rates. However, sites of exuberant hemorrhage can be difficult or impossible for lesion localization and treatment. Colonoscopy can similarly both diagnose and treat sources of hemorrhage, but visualization can be markedly impaired or impossible without bowel preparation in the presence of substantial stool burden. For the small bowel, capsule endoscopy is the primary endoscopic method, although advanced conventional endoscopic techniques can be used to visualize the proximal and distal segments of small bowel. Unfortunately, capsule endoscopy is a purely diagnostic modality without therapeutic benefit, with only moderate sensitivity and specificity for identification of the bleeding source within small bowel.

Similar to endoscopy, conventional angiography also allows both diagnosis of active GI hemorrhage as well as effective treatment capability. Conventional angiography is considered the gold standard radiologic modality for the detection of active GI bleeding. Whereas for endoscopy, some parts of the small bowel are difficult to thoroughly assess due to the range of the endoscope, the entire GI tract is accessible to angiography. Despite this, there are some disadvantages to conventional angiography. While angiography is a minimally invasive procedure, an arterial puncture may be a source for complications in some patients. Additionally, depending on the depth of sedation, patients may not be able to cooperate with breath-holding, which can negate the benefits of digital subtraction angiography and render the study less sensitive. Finally, angiography is the least sensitive study for the detection of GI bleeding. The threshold rate of active hemorrhage for angiographic visualization has been reported to be in the range of 0.5 to 1 mL per minute. Thus, despite the fact that active hemorrhage may be occurring, the angiographic study will be negative if the bleeding is below the threshold rate for visibility.

When a site of active extravasation is visualized during the angiographic study, attempts at embolization can be performed for definitive management. While microcoils are the current standard material for embolization, a variety of materials have been utilized, including liquid embolics, particles, gelfoam, and autologous clot. In order to minimize risk of bowel ischemia, generally, embolization is performed as distally as feasible. Based on a systematic review of the literature comprising 819 patients with upper GI bleeding, Loffroy et al. reported that the clinical success rate ranged from 44% to 94% (average 67%) in patients who had technically successful embolization. In a recent study on embolization for lower GI hemorrhage, the clinical success rate was 75%. Finally, whereas endoscopic evaluation can sometimes identify the source of GI hemorrhage even in the absence of active extravasation, angiography is diagnostically effective only in the setting of active extravasation. Thus, if intermittent GI hemorrhage has ceased upon performance of angiography, the study will be negative and therefore of no diagnostic value and treatment cannot be performed.

**Occult GI Bleeding**

Occult GI bleeding is defined as constant or recurrent hemorrhage from an unknown GI origin in the setting of negative diagnostic studies. There are two general subtypes of occult bleeding. In one, the site of bleeding is unknown because the hemorrhage is occurring at such a slow rate that detection is challenging or impossible with scintigraphy, CTA, or capsule endoscopy. These patients often present with melena or heme-positive stool samples, with chronic anemia and need for occasional intermittent transfusions. Hemorrhage may be occult on endoscopy due to their location and occult on radiologic studies due to their slow rate of bleeding that are below the threshold for detection with radiologic methods. Sites within the colon or upper GI tract that are accessible to upper and lower endoscopy are usually able to be identified even in the absence of active bleeding, since nonbleeding lesions such as ulcers, masses, and vascular lesions are typically easily visualized. A different type of occult GI bleeding can be quite brisk but occult in origin due to its intermittent nature. These hemorrhages can in fact be quite massive but with onset of hemostasis that occurs effectively soon after initiation and prior to radiologic imaging, resulting in negative studies. With occurrence of intrinsic fibrinolysis, relaxation of vasoconstriction, and/or re-injury, the acute onset of hemorrhage may reoccur. Despite being transient, episodes of hemorrhage can be so massive that the patient may become have symptomatic hemorrhage shock, requiring hospital admission and blood transfusions. These patients typically undergo both endoscopic and radiologic evaluation; however, depending on timing, then all studies may be negative, and the patient may be discharged once stabilized, only to undergo additional episodes in the future.

**Mechanism for Hemostasis**

The physiology of arterial hemostasis forms the premise of provocative angiography. Arteries contain muscular layers that have the ability to contract, which results in decrease of the luminal diameter. This phenomenon is well known to angiographers, who often experience arterial vasospasm in response to irritation of the endothelium by a guidewire or catheter. In the response to arterial injury, the purpose of reflex vasoconstriction is to physi-
cally limit the rate of blood loss from the injured artery. The more complex component of hemostasis is the coagulation cascade, where coagulation proceeds through a series of proteolytic reactions that culminates in generation of sufficient thrombin to form a fibrin clot. When the artery wall or intima is injured, the underlying integral membrane protein called ‘tissue factor’ is exposed to the circulating blood, with which circulating plasma factor VIIa forms a complex and thereby initiates the coagulation cascade that results in the fibrin clot that obstructs the ‘hole’ in the injured artery. While vasospasm serves to minimize the volume of blood loss, the resulting stagnation of blood flow also encourages thrombosis of the entire vessel, particularly when the vessel is small, which serves as a mechanism for long term termination of hemorrhage.

**Provocative Mesenteric Angiography**

The concept of intentional pharmacologic provocation of GI hemorrhage was first described by Rosch et al who described it as pharmacoangiography in 1982. In this case series on 3 patients, the authors described administering intravenous heparin, intra-arterial tolazoline (vasodilator), or intra-arterial streptokinase separately in a variety of circumstances in patients with occult GI hemorrhage undergoing angiography. In the three reported cases, visualization of a site of active extravasation occurred after previously negative studies, that then allowed surgical addressment of the bleeding site.

The premise of provocative angiography is based on opposing components of the natural process of hemostasis. The vasodilator serves to counteract the arterial vasospasm, and in doing so, potentially accomplishes two important goals: (1) increases blood flow through the vessel, which results in increased delivery of subsequent thrombolytic medication; (2) an increased rate of contrast extravasation when selective angiography is performed, thus optimizing chances for visual detection of active extravasation. Tissue plasminogen activator (tPA) is a serine protease that binds to plasminogen and cleaves it into plasmin, which then degrades fibrin clots. Thus, by administering tPA into the target artery, the process of fibrinolysis is initiated with the goal of resolving thrombus within injured artery and to cause dissolution of the fibrin plug obstructing the actual ‘hole’ in the injured arterial wall. Systemic heparinization is the final crucial component that prevents rethrombosis after bleeding has been reestablished, as tissue factor at the site of arterial injury will be re-exposed to circulating blood that may induce fibrin plug reaccumulation or thrombosis.

**Efficacy of provocative mesenteric angiography**

Subsequent to the initial report of pharmacoangiography, there have been a number of additional case reports and case series on the topic. In 1987, Ková et al reported the use of one or more of the provocative agents (heparin, heparin plus tolazoline, or heparin plus tolazoline, and streptokinase) in 10 patients with negative prior studies, with an 80% positivity rate. They utilized a strategy of progressively aggressive attempts, starting with heparin alone (n = 2), followed by tolazoline if negative (n = 7), followed by additional streptokinase if still negative (n = 2). In 2000, Bloomfeld et al reported the use of tolazoline, heparin, and/or urokinase in 7 patients, with two resulting in positive studies, allowing both to undergo surgical therapy. In 2001, Mernagh et al reported the use of intravenous heparin alone in 12 patients who had just undergone a negative mesenteric angiogram. In half of these patients, the source of GI bleeding was determined with angiography, and subsequently managed surgically or endoscopically. Ryan et al reported in 2001 the first use of provocative angiography in order to allow definitive treatment via superselective embolization. In this study, heparin, intra-arterial tolazoline, and intra-arterial tPA were utilized. Provocation was successful in 8 of 16 patients (50%). Three of these patients were treated successfully with superselective embolization. Widius and Salis, in 2007, described using reteplase alone in 9 patients with negative previous studies, with 8 of 9 studies (88.9%) resulting in active extravasation, allowing attempts at superselective embolization. The high positivity rate may be due to the high dose of reteplase utilized, which is equivalent to 25 mg of tPA administered up to twice. However, in 2 patients, hemorrhage ceased before embolization could be performed notably, heparin was not utilized in these patients. In 2010, Kim et al reported utilizing heparin, nitroglycerin, and tPA in 36 cases with occult GI bleeding, with identification of the source of hemorrhage in 12 (33%). Nine underwent successful superselective embolization and one underwent resection of a small bowel mass. In this study, the authors analyzed predictors of success, finding that patients with melena were less likely to have a positive study than those with hematochezia, and patients admitted for reasons other than acute lower GI hemorrhage were also less likely to have a positive study. Additionally, patients who underwent prior angiography were more likely to have a positive scan. In aggregate, the authors proposed that the underlying explanation was that patients with massive intermittent episodes of GI bleeding were more likely to yield positive results with provocative mesenteric angiography than patients with slow chronic GI bleeds.

**Safety of provocative angiography**

The safety of provocative angiography is a critical issue, because administration of thrombolytic agents are technically contraindicated in patients with a recent history of GI hemorrhage. Not only are these patients at risk of the usual systemic risks of hemorrhage with administration of thrombolytic agents, they are also at theoretical risk for uncontrollable GI hemorrhage at the site of arterial injury. Within the above series that were reported in the era of microcoil embolization, there were no cases reported of uncontrollable hemorrhage and no remote sites of hemorrhage were encountered. The reason for the safety may be attributable to the fact that both thrombolytics and vasodilators are metabolized by the liver. Therefore, there is a high first-pass effect, since essentially 100% of the medication administered into a mesenteric artery perfuses the capillaries, and drains via the portal venous system into the liver where it is metabolized. Due to the high first pass effect with infusion into a mesenteric artery, the concentration of medication that reaches the systemic circulation is markedly less than if administered intravenously. A second major point is that the amounts of tPA administered in the studies is less than what is typically administered systemically in the case of myocardial infarction (100 mg), pulmonary embolism (100 mg), and stroke (63 mg). Even at these high systemic concentrations, the risks of systemic hemorrhagic complications are low. In a large study on 3,272 patients who were administered 100 mg of tPA intravenously, the incidence of intracranial hemorrhage was 0.4%. Despite these theoretical reasons for safety, two specific clinical scenarios should be avoided. Patients with a recent GI anastomosis may be at risk for uncontrollable GI hemorrhage arising from multiple vessels around the anastomosis that could require embolization for management which could lead to ischemia and dehiscence of the anastomosis. Secondly, great caution should
be undertaken in patients with cirrhosis and portal hypertension. After administration of tPA into mesenteric vessels, there could be accumulation and increasing concentrations within the stagnant portal system. If the source of prior hemorrhage were via gastric or esophageal varices, massive hemorrhage could ensue, and the catheter system within the mesenteric arteries would be futile for management. Rapid identification of the underlying portal venous source would need to occur in order to institute the appropriate therapy (endoscopy, transjugular intrahepatic portosystemic shunt, balloon-occluded retrograde transvenous obliteration, etc.). Therefore, it is prudent to have a contrast-enhanced computed tomography (CT) prior to performing provocative angiography to search for varices and other signs of portal hypertension.

**Provocative angiography protocol**

At the author’s institution, all available endoscopic and radiologic studies are first reviewed, as well as the clinical history. If the history suggests a low constant hemorrhage manifesting as melena with anemia and intermittent need for transfusions less than once per week, then provocative angiography is deemed of low yield, because the rate of hemorrhage would be too slow to visualize angiographically, even if active hemorrhage is provoked. The ideal candidate for provocative angiography is one who has had repeated episodes of intermittent massive hemorrhage but with repeatedly negative studies. Patients are screened for the usual contraindication for thrombolytic therapy. A contrast-enhanced CT scan of the abdomen within the preceding 6 months is required. Patients with a history or suspected portal hypertension are relatively contraindicated. Patients with a recent GI anastomosis within 3 months are absolutely contraindicated.

If any prior study has demonstrated the site of hemorrhage, then the corresponding mesenteric artery is targeted (i.e., celiac artery, superior mesenteric artery [SMA], or inferior mesenteric artery [IMA]). If more detailed localization information is known, then a more distal branch artery will be the target site (particularly with a positive CTA). All patients should have undergone upper and lower endoscopy, CT angiography, and scintigraphy. If all radiologic studies are negative, and both upper and lower endoscopy are negative, then the presumed site of bleeding is small bowel (due to the excellent sensitivity for endoscopy to visualize lesions in the stomach and colon), and therefore the default target artery is the SMA.

After angiography of the celiac, SMA, and IMA are performed and deemed negative, then the provocative angiography protocol is initiated. 5,000 units of heparin is administered intravenously, with a goal activated clotting time (ACT) of greater than 200 seconds. Heparin is administered in bolus form intermittently to maintain the target ACT. For the celiac or SMA, 200 µg of nitroglycerin in 10 mL of saline is administered into the target artery over the course of a minute, followed by 8 mg of tPA in 20 mL of saline infused intra-arterially over the course of two minutes. After waiting 10 minutes, angiography is performed. If active extravasation is visualized, then attempts are then made to perform superselective embolization (Fig. 1). In cases where the site of active bleeding ceases while gaining superselective microcather position, then additional vasodilator and tPA are administered to reactive bleeding. If the angiogram is negative, then the process is repeated with another 200 µg of nitroglycerin and 12 mg of tPA.

If again negative, then a third and final infusion is performed, consisting of 200 µg of nitroglycerin and 24 mg of tPA. If no active extravasation is visualized, then the study is deemed negative. For the IMA, half doses are utilized. For more selective arteries, even smaller doses are used commensurate with the arterial distribution. Upon completion, the sheath is removed, with hemostasis achieved with manual compression or an arterial closure device. At the author’s institution, we have not encountered issues with access site complications despite the intra-arterial thrombolytic.

In the setting of a negative provocative mesenteric angiogram, the patient is expected to have active GI bleeding, but presumably at a rate too slow to visualize angiographically. Consideration is given to sending the patient for CTA or scintigraphy for localization, if no localization information has been previously obtained. Given the assumption that the active hemorrhage is too slow to visualize angiographically in patients with a negative study, the patient is not considered a candidate for subsequent mesenteric angiograms, unless the quantity of hemorrhage markedly increases above and beyond their usual presentation, or if they become hemodynamically unstable during an episode of GI bleeding.

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**Fig. 1.** A 76-year-old patient with multiple recurrent episodes of massive bright-red lower gastrointestinal (GI) bleeding, with two prior negative conventional arteriograms. One of two previous tagged red blood cell scans were positive for active bleeding in the region of the hepatic flexure. (A) Initial superior mesenteric artery (SMA) arteriogram is negative for active extravasation. (B) After administration of 5,000 units of intravenous heparin as well as intra-arterial injection of 200 µg of nitroglycerin and 8 mg of tissue plasminogen activator into the SMA, there is active extravasation at the hepatic flexure (arrow). (C) After superselective coil embolization (arrow), there is no further extravasation. The patient had no subsequent episodes of GI bleeding.
Provocative Scintigraphy

In several case reports, intravenous heparin administration was used successfully to elicit a positive tagged red blood cell scintigraphy in patients with previously negative studies. More recently, in a patient with occult GI bleeding despite numerous tests, the authors administered intravenous heparin prior to performing Tc-RBC scintigraphy with single-photon emission CT (SPECT)/CT, which allowed successful identification of hemorrhage in the distal ileum that was subsequently confirmed surgically. In the largest series, in 1998, Malden et al reported using combined SPECT/CT, which allowed successful identification of hemorrhage in the distal ileum that was subsequently confirmed surgically. In the largest series, in 1998, Malden et al reported using combined SPECT/CT, which allowed successful identification of hemorrhage in the distal ileum that was subsequently confirmed surgically. In the largest series, in 1998, Malden et al reported using combined SPECT/CT, which allowed successful identification of hemorrhage in the distal ileum that was subsequently confirmed surgically.

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