Pharmacologic provocation combined with endoscopy in refractory cases of GI bleeding

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Background and Aims: The source of GI bleeding may elude us despite exhaustive testing in some cases. Bleeding in these cases is often related to a vascular lesion that is discernible only when actively bleeding. The objective of this study was to determine the efficacy and safety of endoscopy combined with the administration of antiplatelet and/or anticoagulant agents to stimulate bleeding in order to define a source.

Methods: A retrospective review of a database of device-assisted enteroscopy (DAE) procedures was completed to identify cases in which provocation with antiplatelet or anticoagulant agents was used as part of a GI bleeding evaluation. Procedures were divided into 3 groups based on the method of provocation: patients with a history of bleeding associated with an antiplatelet/anticoagulant (*provocation-experienced*); patients naïve to these medications (*provocation-naïve*); and cases of recurrent, overt GI bleeding in which a combination of clopidogrel and intravenous heparin was administered for provocation (*Lousiana State University [LSU] protocol*).

Results: A review of 824 DAE procedures was completed to identify a total of 38 instances in which provocation was attempted in 27 patients. These cases were subdivided into 13 provocation-experienced procedures, 18 provocation-naïve procedures, and 7 LSU protocol procedures. The diagnostic yield of provocative testing per procedure was 53% in the provocation-experienced group, 27% in the provocation-naïve group, and 71% in the full protocol group. Provocative testing was revealing in 15 of 27 patients; angioectasias and Dieulafoy lesions were the most common pathologies. Provocative testing was not beneficial in 4 patients who were eventually diagnosed with bleeding caused by intestinal angioectasias (3) and an aorto-enteric fistula (1). There were no adverse events.

Conclusions: Provocative testing combined with endoscopy can be justified as an option in the diagnostic algorithm of complex cases of GI bleeding when intermittent bleeding related to a vascular lesion, such as an angioectasia or Dieulafoy, is suspected. However, this novel technique should be considered only after standard management has failed to define a bleeding source, and bleeding continues to recur. This is the first reported case series of provocative testing combined with endoscopy. (Gastrointest Endosc 2017;85:112-20.)

(footnotes appear on last page of article)

GI bleeding is a frequent cause of inpatient hospitalization resulting in over 500,000 admissions annually.[1] Obscure GI bleeding (GIB) has been defined in the past as bleeding, the cause of which is undefined despite evaluation by standard upper endoscopy and colonoscopy.[2] When this previous definition is used, obscure GIB accounts for 5% of bleeding presentations, most of which originate in the small bowel.[2] Obscure GIB has recently been redefined as bleeding that is obscure in origin despite the current standard of care evaluation including small-bowel study by video capsule endoscopy (VCE) and/or device-assisted enteroscopy (DAE) and radiographic studies in addition to standard endoscopy.[3] Because a bleeding source is often discovered after completion of these additional examinations, the number of cases of truly obscure bleeding is likely to account for less than 1% to 2% of all cases of GI bleeding. Obscure GIB by either definition should be subclassified as occult bleeding, as manifested by iron deficiency anemia and/or fecal occult blood test (FOBT) positive stool or overt bleeding, as manifested by symptoms of melena or hematochezia. In some instances, the source of bleeding may be successfully localized to a specific segment of the GI tract, such as

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the small intestine, but the cause of bleeding remains unknown or obscure. In patients with a previous history of symptomatic angioectasias, bleeding from angioectasias is likely and may no longer be considered obscure.

In patients with obscure GIB or suspected bleeding from angioectasias, blood loss is commonly related to vascular lesions, such as Dieulafoy lesions or angioectasias, which may be difficult or impossible to detect unless actively bleeding.[4,5] Our endoscopy unit has accumulated a large number of cases of refractory GI bleeding through referral for DAE. In highly selective cases, we have pursued provocative testing including the administration of an antiplatelet and/or anticoagulant agent to elicit bleeding combined with endoscopy, in order to delineate a bleeding source. The purpose of this study is to describe this experience with the use of provocative endoscopy in the management of cases of refractory GI bleeding.

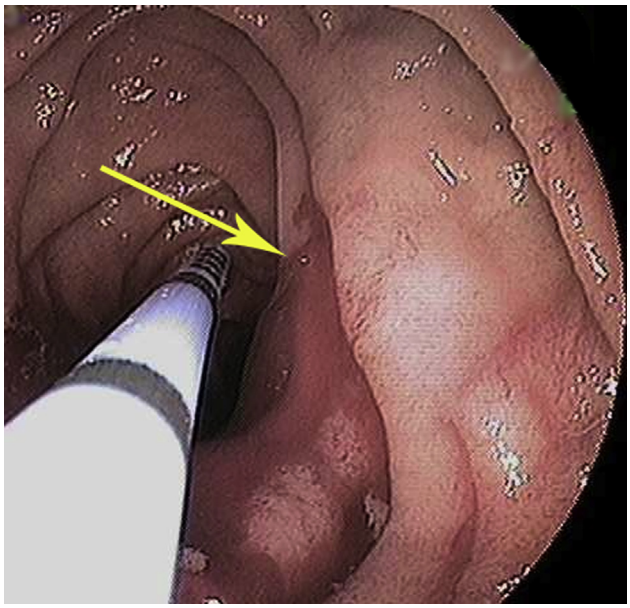

Figure 1. Active pulsatile bleeding associated with a small-bowel Dieulafoy lesion.

METHODS

This case series was designed as a single-center retrospective review. Institutional review board approval was obtained before study initiation. A database of DAE procedures performed between October 4, 2007, and October 31, 2015, was reviewed to identify cases in which provocation was used in the management of obscure GI bleeding. Provocative cases were defined by the administration of an antiplatelet and/or anticoagulant agent for the purpose of stimulating bleeding followed by the performance of an endoscopic procedure. The endoscopic procedure selected may vary based on the results of each patient's previous evaluation. For example, patients with a history of bleeding from the proximal jejunum identified by VCE could be selected for provocation with anterograde DBE. In patients in whom the bleeding segment was unknown, a VCE study could be chosen as the next endoscopic procedure in order to first localize the bleeding segment. Successful provocation was defined as endoscopic documentation of active bleeding in response to antiplatelet or anticoagulant administration.

Vascular lesions, such as angioectasias or Dieulafoy, were the suspected bleeding source in these cases. Angioectasias were defined as dilated submucosal veins accompanied by ectasia of the overlying mucosal venules and capillaries.[6] Macroscopically, they have a cherry-red color and typically a fern-like pattern. Angioectasias may be multiple in approximately 50% of cases, whereas Dieulafoy lesions are rarely so.[5-7] Some angioectasias may appear as Dieulafoy-like lesions if actively bleeding. Dieulafoy lesions were defined using the following criteria described by Dy et al[8]: (1) active arterial spurting or micropulsatile streaming from a minute (<3 mm) mucosal defect with normal surrounding mucosa (Fig. 1); (2) visualization of a protruding vessel, with or without active bleeding through a minute defect with normal surrounding mucosa; or (3) fresh, densely adherent clot with a narrow point of attachment to a minute mucosal defect or to normal-appearing mucosa.

Provocative interventions were classified into 3 subgroups based on the method by which the provocative agent was selected and administered, including provocation-experienced, provocation-*naïve*, and full LSU protocol. Patients in the full protocol group were all managed in a specific way with the same provocation agents. Patients in the experienced and naïve groups were managed similarly within their group but not with the same provocation agent in all cases. The primary reason for creating the experienced and naïve subgroups was to evaluate for a higher success rate of provocation in patients with a history of sensitivity to a provocation agent, such as clopidogrel.

(1) Provocation-experienced cases were defined as cases in which a previously prescribed antiplatelet or anticoagulant agent had stimulated bleeding as demonstrated by overt bleeding or precipitation of progressive anemia attributed to GI bleeding. In these cases, the offending agent was reinstituted before endoscopy in attempt to promote active bleeding.
(2) Provocation-naïve cases were defined as cases in which antiplatelet or anticoagulant therapy was initiated in an attempt to provoke bleeding without previous evidence of the effect of these agents on the patient's bleeding pattern.
(3) Full LSU provocation protocol cases were defined as extreme cases of recurrent, overt bleeding that were