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American Journal of Interventional Radiology

Vascular Interventions *Original Research*

Provocative mesenteric angiography for localizing ambiguous gastrointestinal hemorrhage

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Received : 04 May 2021
Accepted : 17 September 2021
Published : 07 October 2021

DOI
10.25259/AJIR_16_2021

Quick Response Code:

ABSTRACT

Objectives: Five percent of patients with recurrent gastrointestinal (GI) hemorrhage have indeterminate origin by radiological and endoscopic examinations. To improve diagnostic accuracy and therapeutic embolization, the technique of provocative mesenteric angiography (PMA) has been developed. It involves the addition of pharmacologic agents to standard angiographic protocols to induce bleeding.

Material and Methods: This is an institutional review board-approved, retrospective study of 20 patients who underwent PMA between 2014 and 2019. All patients had clinical evidence of GI hemorrhage without a definite source. PMA consisted of anticoagulation with 5000 units of heparin and selective transcatheter injection of up to 600 µg of nitroglycerine, followed by slow infusion of up to 24 mg of tissue plasminogen activator into the arterial distribution of the highest suspicion mesenteric artery.

Results: Among the 20 patients who underwent PMA, 11/20 (55%) resulted in angiographically visible extravasation. Of these 11 patients, nine patients underwent successful embolization with coil or glue and were discharged upon achieving hemodynamic stability. Two patients spontaneously stopped bleeding. In our series, PMA resulted in the successful treatment of 9/20 (45%) patients with recurrent hemorrhage. No procedure-associated complications were reported with these 20 patients during the procedure and their course of hospitalization.

Conclusion: In our experience, PMA is an effective and safe approach in localizing and treating the source of GI bleeding in about half of patients with an otherwise unidentifiable source.

Keywords: Bleeding source, Lower gastrointestinal bleeding, Provocative mesenteric angiography

INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is the primary reason for 300,000 admissions per year in the United States alone.[1] With modern imaging and endoscopic techniques, the majority of patients with gastrointestinal (GI) bleeding are appropriately diagnosed and treated. If endoscopic interventions such as upper endoscopy, colonoscopy, enteroscopy, and capsule endoscopy fail to localize bleeding, imaging studies including red blood cell (RBC) tagged scintigraphy, computer tomography (CT) angiography, and conventional angiography are employed. However, up to 5% of these patients will require multiple admissions and blood transfusions despite repeated uninformative radiological and endoscopic examinations.[2] To improve diagnostic accuracy in such

patients, the technique of provocative mesenteric angiography (PMA) has been developed, whereby pharmacologic agents including heparin, nitroglycerine, and tissue plasminogen activator (TPA) are added to standard angiographic protocols to increase the diagnostic yield. It is best employed in patients with recent GI bleeding and allows simultaneous therapeutic embolization. The reported success of this technique in localizing bleeding is <50% in literature.[3] We sought to report our center's experience with provocative angiography while drawing comparisons with similar studies.

MATERIAL AND METHODS

At our institution, an algorithm for the workup of a patient with GI bleeding is generally followed. Patients with acute massive LGIB and hemodynamic instability undergo emergent angiography, whereas those in stable conditions undergo attempts at localization of bleeding with endoscopy, RBC scintigraphy, CT angiography, and formal angiography. Surgery is generally reserved for patients with localized and recurrent bleeding that failed endoscopic and angiographic therapies or emergently in patients with ongoing bleeding and/or hemodynamic instability with or without localization. Our interventional radiology department includes three operators.

This is a retrospective study approved by the institutional review board at our institution. Twenty patients (14 males six females) with a mean age of 72.4 years (range 53–97 years) underwent 22 PMAs between 2014 and 2019. [Table 1] for patient demographics and clinical characteristics at the time of presentation. All patients had occult GI hemorrhage and have undergone multiple negative prior endoscopies, RBC scans, CT angiographies, and mesenteric angiograms. They all had negative angiograms prior to provocation. All included patients underwent PMA. This article specifically addresses the management of patients with GI bleed whose source could not be identified with other exhaustive workups. As such, the rate of identifying patients with overall bleed via angiography is irrelevant.

Mean presenting hemoglobin/hematocrit were 9.2/28.5, respectively. Sixteen patients were transfused with one or more units of packed red blood cells (PRBCs) prior to provocative angiography (mean: 2.55). All patients underwent extensive workup to localize the source of bleeding [Table 2]. All 20 patients underwent previous endoscopic procedures in the following order (total number, mean number per patient): upper endoscopy (n = 38, mean: 1.90), colonoscopy (n = 29, mean: 1.45), wireless capsule endoscopy (n =16, mean: 0.80), and double-balloon enteroscopy (n = 7, mean: 0.35).

Of the 20 patients who underwent PMA, 17 had one or more CT angiographies (n = 24, mean: 1.20) and 7 of 22 patients underwent RBC scintigraphy study (n =10, mean: 0.50). The majority of these radiographic and endoscopic procedures provided low diagnostic yield in terms of localization of the GI bleed.

Table 1: Patient demographics and clinical characteristics at the time of presentation.

S. No.	Age	Sex	BMI	Reason for admission*	Hematocrit	Hemoglobin
1.	72	M	17.48	LGIB	17.1	5.6
2.	69	M	28.62	UGIB	23.2	7.8
3.	62	M	29.37	UGIB	30.5	9.8
4.	53	F	18.73	UGIB/LGIB	34.6	9.9
5.	56	M	23.21	LGIB	21.9	7.2
6.	70	M	30.59	LGIB	36.3	11.6
7.	74	M	18.88	LGIB	25.1	8.3
8.	85	M	20.42	LGIB	31.2	9.9
9.	78	M	19.7	UGIB	36.2	11.2
10.	71	M	31.12	LGIB	35.1	11.7
11.	79	M	19.57	LGIB	23	7.8
12	76	M	34.5	UGIB	29.7	9.6
13.	84	M	27.6	UGIB/LGIB	25	8.3
14.	79	F	20/37	UGIB	31.1	9.8
15	68	F	27.8	LGIB	24.6	7.3
16.	97	M	24	LGIB	34.8	11.3
17.	52	F	19.32	UGIB	32	10.1
18.	83	M	25.8	LGIB	25.5	8.3
19.	59	M	26.37	LGIB	20.9	6.8
20.	81	F	29.27	LGIB	33	11

LGIB: Lower gastrointestinal bleed, UGIB: Upper gastrointestinal bleed

Table 2: Treatment and workup of patients with GI bleed.

S. No.	# of admissions for bleeding	# of PRBC transfusions	# of prior CT angiographies	# of RBC scintigraphies	# of provocative angiographies	# of upper endoscopies	# of colonoscopies	# of capsule endoscopies	# of double balloon endoscopies
1.	2	3	2	1	1	2	3	1	1
2.	1	1	2	0	2	4	0	0	0
3.	1	3	0	1	1	0	1	1	0
4.	2	2	1	0	1	0	0	4	2
5.	1	2	2	0	1	0	2	0	0
6.	1	0	1	0	1	0	1	0	0
7.	2	3	1	0	1	1	1	0	0
8.	3	2	0	1	2	1	1	0	0
9.	1	3	1	2	1	4	3	2	0
10.	2	7	2	0	1	2	3	1	0
11.	1	5	0	0	1	1	1	1	0
12.	2	2	1	0	1	1	0	1	0
13.	1	3	1	0	1	1	1	0	0
14.	4	3	1	0	1	1	0	1	1
15.	4	2	3	2	1	4	1	1	3
16.	3	0	1	0	1	0	3	0	0
17.	4+	0	1	0	1	12	0	0	0
18.	2	5	1	2	1	1	2	1	0
19.	2	5	1	1	1	1	2	1	0
20.	4+	0	2	0	1	2	4	1	0

GI: Gastrointestinal, PRBC: Packed red blood cell, CT: Computer tomography, RBC: Red blood cell

PMA consisted of administration of sequential boluses of intravenous systemic anticoagulation with 5000 units of heparin and selective transcatheter injection of up to 600 μg of nitroglycerine, followed by slow infusion of up to 24 mg of TPA into the arterial distribution of highest suspicion mesenteric artery. As the source of bleed was usually unknown at the time of presentation, the superior mesenteric artery (SMA) was initially targeted for injection with TPA due to its coverage of the largest bowel territory. Provocative agents were administered incrementally over time until active extravasation was visualized or until the interventional radiologist deemed the outcome negative [Table 3]. If no active extravasation was visualized from the SMA despite provocative maneuvers (i.e., after injection of the entire dose of TPA), then the inferior mesenteric artery and celiac arteries were interrogated respectively in all cases.

RESULTS

Among 20 PMAs, 11/20 (55%) resulted in angiographically visible extravasation. Eight out of 11 cases with visualized extravasation underwent successful coil embolization and one patient underwent successful embolization with glue (i.e. 9/11) (45%). Two patients spontaneously stopped bleeding (10%) during the procedure and did not undergo embolization. One of the two patients that spontaneously stopped bleeding was readmitted for recurrent LGIB. On readmission, she underwent wireless capsule enteroscopy, which revealed hypertensive gastropathy without fresh or old blood seen in the stomach. Upper endoscopy and double-balloon enteroscopy again showed hypertensive gastropathy involving the fundus, body, and antrum without evidence of bleeding as well as mild portal hypertensive enteropathy involving the duodenum which was not bleeding. This patient underwent another round of PMA, which was not revealing. She stopped bleeding without further intervention and was discharged.

In 9 out of 20 patients (45%), PMA and coil (n = 8) or glue (n = 1) embolization resulted in the successful treatment of recurrent hemorrhage and discharge from the hospital [Figure 1]. Two out of these nine treated patients were readmitted for GI bleeding. Five of the other nine patients with unsuccessful localization of bleeding during PMA were readmitted for recurrent bleeding. They were transfused with PRBCs and taken for urgent endoscopy and other procedures to identify the source of bleeding. None of these five patients who were readmitted for re-bleeding underwent any further PMA [Figure 2].

DISCUSSION

With 300,000 patients annually admitted to hospitals for GI bleeding, successfully localizing and treating the hemorrhage

Table 3: Provocative angiography details.

S. No.	Artery injected	Dose of heparin (units)	Dose of nitroglycerin (mcg)	Total dose of TPA (mg)	Number of angiography cycles for TPA	PMA resulted in extravasation	Bleeding source	Bleeding lesion	Coil or glue embolization resulted in bleeding discontinuation
1.	SMA	5000	0	24	3	No	-	-	No
2.	Celiac A	5000	200	20	2	No	-	-	No
3.	SMA	5000	200	24	3	Yes	Colon	Diverticular	Yes
4.	SMA	5000	200	24	3	Yes	Small bowel	AVM	No
5.	SMA	5000	0	20	3	Yes	Colon	Diverticular	Yes
6.	SMA	5000	400	24	3	Yes	Colon	Diverticular	No
7.	SMA	5000	200	24	3	No	-	-	No
8.	IMA	5000	100	16	3	Yes	Colon	Diverticular	Yes
9.	SMA	5000	200	16	2	Yes	Small bowel	Diverticular	Yes
10.	IMA	5000	200	24	3	No	-		No
11.	Celiac A	5000	400	16	2	Yes	Small bowel	AVM	Yes
12.	Celiac A	5000	600	24	3	No	-		No
13.	SMA	5000	600	24	3	Yes	Colon	Diverticular	Yes
14.	SMA	5000	200	24	3	No	-		No
15.	SMA	5000	0	24	3	No	-		No
16.	IMA	5000	200	12	2	Yes	Colon	Diverticular	Yes
17.	SMA	5000	0	24	3	No	-		No
18.	SMA	5000	400	16	2	Yes	Colon	Diverticular	Yes
19.	SMA	5000	200	16	2	Yes	Colon	Diverticular	Yes
20.	SMA	5000	600	24	3	No	-		No

PMA: Provocative mesenteric angiography, TPA: Tissue plasminogen activator, SMA: Superior mesenteric artery, CA: Celiac artery, IMA: Inferior mesenteric artery, AVM: Arteriovenous malformation

is of utmost importance. Although most patients are successfully managed, 5% have recurrent hemorrhage leading to multiple blood product transfusions, several hospital admissions, and numerous diagnostic tests.[1]

The patients in our institution had undergone multiple transfusions and diagnostic workups. Recurrent and difficult to locate GI bleeding caused patients to undergo a mean of 2.13 hospital admissions and 2.54 PRBC transfusions as well as a spectrum of other diagnostics including upper endoscopies, colonoscopies, capsule endoscopies, tagged RBC nuclear medicine scans, CT angiographies, and formal angiographies. By using PMA after a negative workup, we hope to increase diagnostic accuracy and help decrease the clinical and financial strain of GI bleeds on patients, and reduce emergency room visits and readmissions.

PMA has been shown to be an effective method in localization and subsequent treatment of GI bleeding. A review of prior studies on PMA yielded six case series and three case reports with a total of 82 patients.[3-10] The pooled extravasation and successful definitive therapy rates in these studies were 44% (36/82) and 37% (30/82) respectively. In our study, administration of pharmacologic provocative agents including heparin (5000 units), TPA (mean: 18.9 mg), and nitroglycerin (mean: 263 μg) followed by angiography resulted in 55% (11/20) extravasation and 45% (9/20) therapy rate, which falls within the range found in the literature (22–55%). Of the 11 patients who had extravasation, 8 (72%) had bleeding in their colon, nine (81%) of the bleeds were due to diverticular disease, and 2 (18%) were due to arteriovenous malformation. In none of our 20 patients did heparin and nitroglycerin alone induce extravasation, highlighting the importance of adding safe and therapeutic doses of TPA to induce extravasation. Therapy was carried out by way of embolization with coil in eight patients and glue in one patient. To the best of our knowledge, no hemorrhagic or procedure-associated complications related to thrombolytic therapy were identified in any of our twenty patients, which demonstrates the safety of this procedure.

Similar to our study, Kim *et al*.[3] published the most informative series with 34 patients. Their study found a 31% (11/36) rate for both extravasation and successful therapy. In another study with nine patients, Widlus and Salis[4] successfully identified bleeding in 89% (8/9) of patients and successfully embolized 55% (5/9). They proposed that their high rate of identification was likely due to acuity of illness in their patients who had evidence of recent massive hemorrhage and thus likely re-bled with limited provocation. They administered Reteplase to their patients instead of TPA at an initial dosage of 5 units and a repeat dosage of 5 units if bleeding was not seen. This dosage of Reteplase is equivalent to 25 mg of TPA. The use of the more potent Reteplase may point to higher dosages yielding a higher rate of bleeding.

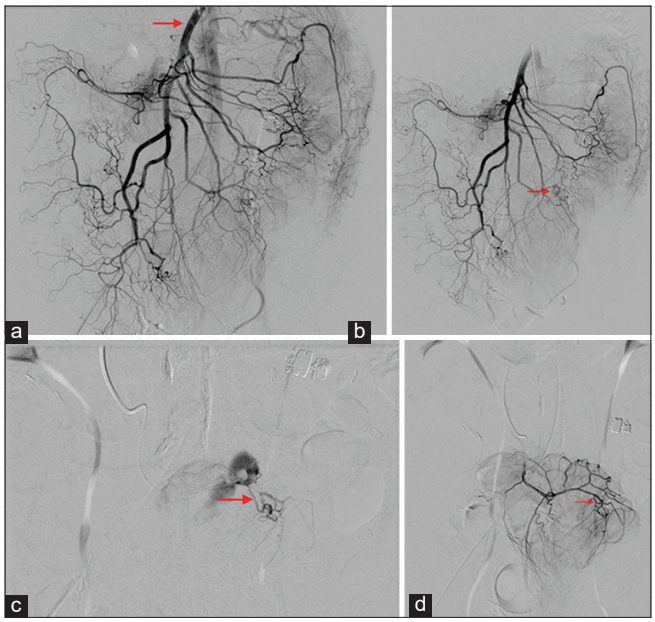

Figure 1: A 77-year-old woman with recurrent GI bleed requiring multiple transfusions and ICU admission. (a) Superior mesentery arteriogram. Arrow points to the origin of SMA. (b) Following provocative infusion with intravenous heparin, nitroglycerin, and TPA, a fourth-order branch of the SMA to the distal jejunum had active extravasation. Arrow points to the extravasation. (c) Super selective embolization. Arrow points to superselected vessel of concern prior to coil embolization. (d) No extravasation post embolization. Arrow points to the site of embolization. GI: Gastrointestinal, SMA: Superior mesenteric artery, TPA: Tissue plasminogen activator.

Our study possesses a number of strengths; including a relatively larger number of patients (n = 20) and relatively higher extravasation (55%) and therapeutic (45%) rates compared to those reported in the literature, presumably due to higher safe doses of TPA administration than those reported in the literature. There are several limitations to our study. Although it is on the larger end of similar studies, it only includes 20 patients. With such a relatively small sample size it is difficult to draw definitive conclusions or draw up a solid protocol in the workup of patients with GI bleed that incorporates PMA. Selection bias is another limitation of our study as our patients are only those referred to us by other providers. Another limitation of the study is that it is a retrospective review of treatments without set guidelines. As there was no set protocol or guideline regarding the timing of PMA, these were performed at the discretion of the practicing interventional radiologists. The dosages also differed between patients; some were given 12 mg of TPA and others received incrementally higher doses up to 24 mg. In gaining more comfort and experience with this technique, we suggest that a study protocol should be designed incorporating PMA in the workup and treatment of recurrent GI bleed. Different dosages of the drugs can be investigated to determine the highest effective dose without compromising

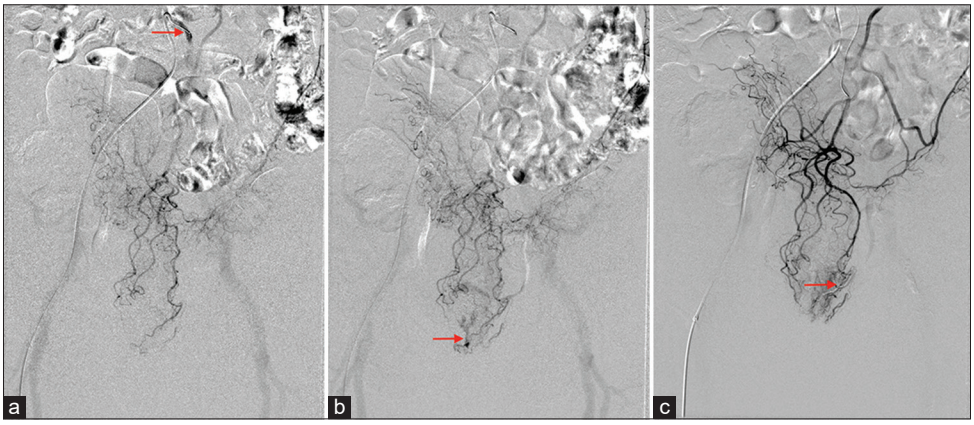

Figure 2: A 96-year-old male with recurrent colonic diverticular bleed. (a) Inferior mesenteric arteriogram. Arrow points to the origin of IMA. (b) Provocative infusion with heparin, nitroglycerin, and TPA revealing extravasation from the superior rectal artery branch of the IMA. Arrow points to extravasation. (c) No active hemorrhage following coil embolization of a third-order branch of the superior rectal artery. Arrow points to the site of embolization. IMA: Inferior mesenteric artery, TPA: Tissue plasminogen activator.

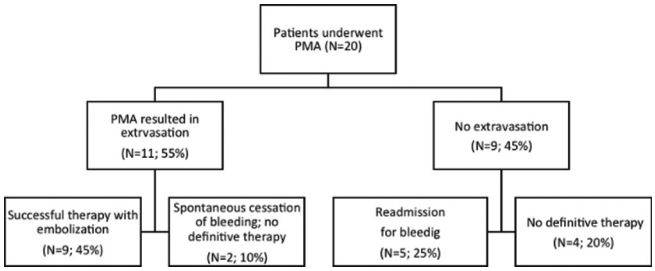

Figure 3: Patient Flow Digram

safety. Individual practitioners should note that according to the Food and Drug Administration, intentionally provoking bleeding to pinpoint the source of the extravasation is not an approved indication for the use of TPA.

Overall, our results show that PMA with embolization is effective and safe in localizing and treating occult GI bleeds. We found that the minimum dose of TPA required to successfully induce bleeding was 12 mg, which is below the recommendation of 100 mg TPA for pulmonary embolism.[11] This allows for the potential of increasing the amount of TPA administered with increases in extravasation and therapy.

CONCLUSION

Our findings suggest that PMA is a valuable, minimally invasive technique that could be incorporated into clinical practices to localize and treat recurrent and ambiguous GI bleeds. Given the paucity of guidelines and controlled studies, further prospective studies are needed to validate the efficacy and safety of this procedure and assist in the drafting of protocols.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Kohanteb PA, Lipshutz HG, Okonkwo B, Oka K, Kasheri E, Cohen J, *et al*. Provocative mesenteric angiography for localizing ambiguous gastrointestinal hemorrhage. Am J Interv Radiol 2021;5:18.