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Original Article

Efficacy and clinical outcomes of angiography and transcatheter arterial embolization for gastrointestinal bleeding in Crohn's disease

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A B S T R A C T

Background: To retrospectively investigate the use of angiography as a diagnostic tool and evaluate technical and clinical efficacy of transcatheter arterial embolization (TAE) in Crohn's disease-related gastrointestinal (GI) bleeding.

Methods: Institutional Review Board approval with waiver of patients' informed consent requirement was obtained. There were 39 angiographies performed in 24 patients (male:female = 18:6, median age = 25 years) presenting with Crohn's disease-related GI bleeding between 2001 and 2014. The technical and clinical success rate of TAE as well as procedure-related complications and 2-year mortality rate were evaluated. Clinical factors such as vital signs and laboratory findings as well as other modalities of investigations were analyzed.

Results: Among 39 angiographies, 25.6% of angiographies were performed as the initial choice of investigation and angiography was performed after endoscopy failed to identify a bleeding site in 33.3%. There were negative angiographic findings in 66.7% (26/39). TAE ($n = 13$) demonstrated 100% technical success rate and 69.2% (9/13) clinical success rate with one case of ischemic complication and one case of mortality due to combined pneumonia. Ileal branches were the most frequent site of embolization and the combination of gelatin sponge slurry and microcoil was most commonly used.

Conclusion: Angiography and TAE may be the initial or follow-up management option in patients with Crohn's disease presenting with acute GI bleeding. Although the rate of negative angiographic findings was high (66.7%), TAE showed high technical success rate and acceptable clinical success rate in patients with positive angiographic findings.

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Keywords: Angiography; Crohn disease; Embolization; Gastrointestinal hemorrhage; Therapeutics

Introduction

Crohn's disease (CD) has been recognized as an established source of gastrointestinal (GI) bleeding and is regarded in CD as disease manifestation. While CD is often associated with mild GI bleeding for which medical management is indicated, acute severe GI bleeding is a rare complication. Acute severe GI bleeding occurs in 0.9% to 6% of patients with this disease and accounts for 1.3% of CD-related admissions.^{1–5}

The source of GI bleeding may be identified by endoscopy, computed tomography (CT), radionuclide bleeding scan and angiography. Endoscopy is generally considered primary choice of investigation in GI bleeding but its role may be limited in CD. The presence of multiple areas of inflammation and strictures in CD may significantly compromise endoscopic evaluation. Moreover,

in the presence of continuous massive bleeding visualization of the bleeding site during endoscopy may not be possible.⁶ Therefore, angiography may be an alternative diagnostic option enabling localization of the bleeding site and offering a therapeutic opportunity with transcatheter arterial embolization (TAE).⁷

For patients with life-threatening GI bleeding and hemodynamic instability, surgical resection remains the standard treatment although significant perioperative mortality and morbidity are inevitable.⁸ Moreover, due to relapsing course of CD, minimal surgical attempts should be made whenever possible to avoid short bowel syndrome.^{9,10} Recent studies report successful control of massive, life-threatening GI bleeding in CD patients by TAE.^{7,11}

The purpose of our study was to retrospectively investigate the use of angiography as a diagnostic tool and evaluate the efficacy of TAE in patients with CD presenting with GI bleeding.

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Methods

Patient characteristics and study design

The study was approved by the Institutional Review Board of Asan Medical Center; informed consent for data usage was waived considering the retrospective nature of the study. Electronic medical records were used. Informed consent was obtained prior to performing angiography and TAE.

We retrospectively collected patients with CD who presented with GI bleeding and underwent angiography. The diagnosis of CD was made based on clinical history, endoscopic and pathologic findings. Patients' vital signs, including blood pressure and heart rate, prior to and after angiography were recorded. Hemoglobin and coagulation profile including prothrombin time, activated partial thromboplastin time, and international normalized ratio were measured prior to angiography. The number of units of packed red blood cells transfused prior to and after angiography and/or TAE was recorded. Types of investigations performed prior to angiography were noted.

Angiography and embolization procedures

Angiography and TAE were performed by three experienced interventional radiologists (G.Y.K., J.H.S., and H.K.K.). Before each procedure, CT scans and endoscopy, if available, were thoroughly reviewed to localize the bleeding site. Using a 5-F catheter (RH catheter; Cook, Bloomington, IN, USA) via the right common femoral artery, celiac artery, superior mesenteric artery, or inferior mesenteric artery angiograms, as deemed necessary by the interventional radiologist, were obtained to determine the focus of the GI bleeding. Superselection of bleeding arteries was performed using a 2-F to 2.4-F microcatheter (Progreat [Terumo, Tokyo, Japan] or Renegade [Boston Scientific, Marlborough, MA, USA]). The selection of embolic materials was based on the preference of the interventional radiologist and availability, and the types of materials were as follows: N-butyl cyanoacrylate (NBCA) (Histoacryl; B. Braun Melsungen AG, Melsungen, Germany) mixed with iodized oil (Lipiodol; Andre Guerbet, Aulnay-Sous-Bois, France), microcoils (Cook), polyvinyl alcohol (PVA) particles (Contour; Boston Scientific, Cork, Ireland), and gelatin sponge slurry (Spongostan; Ferrosan Medical Devices, Søborg, Denmark). Various sizes and types of microcoils were used, and PVA particles with diameters of 150 to 250 μ m and 350 to 500 μ m were used. Gelatin sponge slurry was prepared from gelatin sheets by cutting with a scalpel and scissors and mixing the cut gelatin sponge sheets with contrast agents.

Definition and study endpoints

Technical success of TAE was defined as showing no evidence of bleeding as evaluated by completion angiography. Clinical success of TAE was defined as resolution or improvement of symptoms requiring conservative treatment during 1-month follow-up. Patients who underwent angiography with or without TAE were followed up for 2 years for further episodes of GI bleeding and GI bleeding-related admission and operation. The 2 year mortality rate was also determined.

Statistical analysis

Using descriptive statistics, patient age, sex, vital signs, laboratory findings, interval number of days between admission and

angiography and the number of units of blood transfusions were demonstrated. Technical success, clinical success, and 2-year mortality were also assessed using descriptive methods. PASW Statistics for Windows ver. 18.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were expressed as medians with ranges or interquartile ranges (IQRs). Shapiro-Wilk test was used to test for normal distribution. Paired *t*-test was used to compare clinical factors before and after angiography/TAE, while independent *t*-test and Mann-Whitney U test were used to compare clinical factors between angiography only and TAE group as appropriate. *P*-value < 0.05 was considered statistically significant.

Results

Clinical characteristics

There were 24 patients (male:female = 18:6) with CD who presented with GI bleeding and underwent 39 angiographies between 2001 and 2014. The median age was 25 years at the initial presentation (range, 15–67 years). Four patients presented more than once (range, 2–6 patients) for CD-related GI bleeding. One patient presented 3 times (mean interval, 775 days) and another patient presented 6 times (mean interval, 399.2 days) during the study period. There were 6 patients who underwent a repeat angiography during the same admission and no patients underwent more than two angiographies.

Patients presented with history of hematochezia (*n* = 26), melena (*n* = 6) or both (*n* = 1). Three patients reported bleeding from stomy site and 3 patients reported postoperative bleeding at the median interval of 11 days from the day of operation (range, 2–13 days).

There were 10 cases (10/39, 25.6%) of CD-related GI bleeding, in which the initial choice of investigation was angiography. In 29 cases (29/39, 74.4%), a single or multiple investigations were performed prior to the angiography. Endoscopy including colonoscopy, esophagogastroduodenoscopy, and sigmoidoscopy was performed in 18 cases (46.2%), CT of abdomen and pelvis or enterography in 16 cases (41.0%), radionuclide bleeding scan in 13 cases (33.3%), Meckel's scan in one case (2.6%) and small bowel series in one case (2.6%). Angiography was performed after endoscopy failed to identify a bleeding site in 72.2% (*n* = 13/18) of cases in whom endoscopy was performed.

Systolic/diastolic blood pressure prior to angiography was

Table 1 Clinical Characteristics of Study Patients

Characteristic	Value
Age (yr)	25 (15–67)
Male:female (<i>n</i>)	18:6
Interval between presentation and angiography (day)	2 (0–30)
Investigations prior to angiography (<i>n</i>)	
No investigations	10/39 (25.6)
GI bleeding scan	13/39 (33.3)
APCT, CT enterography	16/39 (41.0)
Endoscopy	18/39 (46.2)
Meckel's scan	1/39 (2.6)
Small bowel series	1/39 (2.6)

Values are presented as median (range), number only, or number (%).

GI, gastrointestinal; APCT, abdominopelvic computed tomography; CT, computed tomography.

104.0/64.0 mmHg (IQR, 98.3–113.8/60.3–69.3 mmHg) in angiography only group and 103.0/63.5 mmHg (IQR, 93.0–111.3/59.8–77.3 mmHg) in TAE group with no statistical difference ($P = 0.56$). There were no statistical differences before and after angiography in both angiography only group and TAE group. There was a statistically significant difference in the heart rate before and after angiography in both angiography only group and TAE group ($P < 0.01$ in both). Heart rate was higher in TAE group (100.0 beats/min; IQR, 86.0–128.8) compared with angiography only group (92.5 beats/min; IQR, 82.0–109.8) prior to the angiography but this was not statistically significant ($P = 0.15$). The median hemoglobin (Hb) was 8.2 g/dL (IQR, 6.9–9.1) and there were no statistical differences between angiography only group and TAE group ($P = 0.87$). Moreover, there were no statistical differences in the coagulation profile between angiography only group and TAE group. The patient characteristics and clinical factors are summarized in Tables 1 and 2.

Angiographic findings

Twenty four patients underwent 39 angiographies in patients with CD presenting with GI bleeding. The median interval between presentation and angiography was 2 days (range, 0–30 days). Angiography showed no evidence of bleeding in 66.7% ($n = 26$) and no attempts of TAE was made. There were extravasation in 30.8% ($n = 12$; Fig. 1) and pseudoaneurysm in 2.6% ($n = 1$; Fig. 2), and TAE was subsequently performed. The angiography to be performed was decided by the interventional radiologist based on the patient's clinical history and results of previous investigations. Superior mesenteric arteriography was performed in all cases, inferior mesenteric arteriography was performed in 71.8% ($n = 28$) and celiac arteriography was performed in 30.8% ($n = 12$).

In 26 cases with negative angiographic findings, 9 cases (34.6%) reported no further episodes of bleeding and 2 cases (7.7%) reported episodes of bleeding but were managed conservatively. Readmission was required in 4 cases (15.4%) and further investigations such as CT, radionuclide bleeding scan and endoscopy were required. One patient underwent endoscopic clipping for hemostasis of the suspicious bleeding foci in the ileum the day after negative angiography. A repeat angiography was required in 5 cases (19.2%) due to recurrent hematochezia despite initially negative angiography at the median interval of 5 days (range, 4–12 days). No patients underwent more than two angiographies. There were 2 cases in which the second angiography demonstrated extravasation and TAE was attempted. Five patients (19.2%) eventually required surgery at the median interval of 12 days (range, 0–76 days).

Technical and clinical outcomes of TAE

The clinical courses of 13 patients who underwent TAE for GI bleeding are summarized in Fig. 3. Technical success was achieved in all patients (100%). Clinical success rate was 69.2% (9/13): 5 patients reported no further episodes of bleeding and 4 patients reported intermittent GI bleeding and were managed conservatively. In one patient, a repeat embolization was required the day after the initial angiography due to unsuccessful control of bleeding. One patient required surgical resection two days following TAE. One patient underwent endoscopic hemoclipping for bleeding in the ileum, and another patient underwent double balloon enteroscopy which showed oozing blood in the jejunum and this was managed conservatively.

There was one case of TAE-related ischemic complication who

had a drop of Hb from 12.1 to 9.6 g/dL over 24 hours the day after TAE. The patient underwent double balloon enteroscopy which showed short segmental ischemia of the proximal jejunum at the site of TAE. The endoscopic biopsy revealed chronic active jejunitis consistent with ischemia.

During 2-year follow-up of patients who underwent angiography with or without TAE, 4 patients (16.7%) required GI bleeding-

Table 2 Clinical Factors of Angiography Only Group and TAE Group before and after Angiography/TAE

Characteristic	Before	After	P-value*
Systolic blood pressure (mmHg)			
Overall	104.0 (95.8–113.8)	106.0 (97.0–114.0)	0.62
Angiography only group [†]	104.0 (98.3–113.8)	105.0 (95.3–108.8)	0.33
TAE group [‡]	103.0 (93.0–111.3)	113.0 (100.0–119.0)	0.15
P-value	0.56	0.09	
Diastolic blood pressure (mmHg)			
Overall	64.0 (60.0–71.8)	67.0 (60.0–73.0)	0.42
Angiography only group [†]	64.0 (60.3–69.3)	65.0 (60.0–70.8)	0.72
TAE group [‡]	63.5 (59.8–77.3)	71.0 (62.0–78.0)	0.43
P-value	0.58	0.12	
Heart rate (beats/min)			
Overall	94.0 (82.0–114.0)	80.0 (71.0–90.0)	< 0.01
Angiography only group [†]	92.5 (82.0–109.8)	80.0 (70.5–90.0)	< 0.01
TAE group [‡]	100.0 (86.0–128.8)	80.0 (74.0–86.0)	< 0.01
P-value	0.15	0.95	
Hemoglobin at presentation (g/dL)			
Overall	8.2 (6.9–9.1)		
Angiography only group [†]	8.2 (6.7–9.2)		
TAE group [‡]	8.3 (6.9–8.9)		
P-value	0.87		
Partial thromboplastin (sec)			
Overall	12.3 (11.6–13.4)		
Angiography only group [†]	12.4 (12.2–13.2)		
TAE group [‡]	11.6 (11.4–13.3)		
P-value	0.72		
International normalized ratio			
Overall	1.1 (1.0–1.2)		
Angiography only group [†]	1.1 (1.0–1.2)		
TAE group [‡]	1.1 (1.0–1.2)		
P-value	0.73		
pRBC units during admission			
Overall	7.0 (4.0–10.0)		
Angiography only group [†]	8.0 (4.0–10.0)		
TAE group [‡]	7.0 (4.0–7.0)		
P-value	0.35		

Values are presented as median (interquartile range).

$P < 0.05$ indicates significant difference.

TAE, transcatheter arterial embolization; pRBC, packed red blood cells.

*Mann-Whitney U test was used.

[†]Negative angiography; [‡]Positive angiography.

Fig. 1. A 47-year-old male with Crohn's disease (CD) presented with history of hematochezia. (A) Superior mesenteric angiogram showed extravastation from the terminal ileal branches. (B, C) Superselective angiogram of the terminal ileal branch was performed and successful embolization was done using gelatin sponge slurry. The patient was readmitted twice with CD-related gastrointestinal bleeding during 2-year follow-up.

Fig. 2. A 23-year-old male with Crohn's disease (CD) presented with hematochezia. The first angiography performed the day after the initial presentation showed no evidence of bleeding but the patient reported recurrent symptoms of hematochezia. The second angiography was performed 11 days after the initial angiography. (A) Superior mesenteric angiogram showed a pseudonaerysm in the proximal jejunal artery. (B) Superselection with microcatheter enabled access to the level of vasa recta and embolization was performed using microcoils. (C) Postembolization angiography confirmed no residual bleeding or pseudoanerysm. The patient underwent a surgical resection due to another episode of CD-related gastrointestinal bleeding 20 months after the successful transcatheter arterial embolization.

related admission and 2 patients required two admissions. Further investigations such as colonoscopy ($n = 1$), GI bleeding scan ($n = 2$) and CT of abdomen and pelvis ($n = 1$) were required. The patient with biopsy proven ischemia died of combined pneumonia 54 days after TAE.

Ileal branches were the most frequent site of embolization ($n = 7$) followed by colic branches ($n = 3$), jejunal branches ($n = 2$) and left and right gastric artery ($n = 1$). Various embolization materials alone or in combination were used to achieve hemostasis: the combination of gelatin sponge slurry and microcoil was used most commonly ($n = 5$) followed by microcoil alone ($n = 3$), gelatin sponge slurry alone ($n = 2$), NBCA ($n = 2$) and PVA ($n = 1$).

Discussion

Our study demonstrated that angiography and TAE may be the initial or follow-up management options in patients with CD presenting with GI bleeding. Although the rate of negative angiographic findings was high (66.7%), TAE, which was attempted with positive angiographic findings, showed 100% technical success rate and 69.2% clinical success rate with one case of ischemic complication and mortality.

In our study, angiography was performed as the initial choice of investigation in 25.6% ($n = 10$) of CD patients presenting with GI bleeding. Endoscopy was the most commonly performed investigation in patients with CD-related GI bleeding who under-

Fig. 3. Clinical course of 13 patients who underwent transcatheter arterial embolization (TAE) for Crohn's disease (CD)-related gastrointestinal (GI) bleeding.

went angiography with or without TAE ($n = 18$, 46.2%). There were 13 cases in which endoscopy failed to visualize the bleeding focus and angiography was subsequently performed. While endoscopy offers direct visualization and potential therapeutic opportunities, its role may be limited in CD-related GI bleeding. The presence of multiple skip lesions of inflammation and stricture in CD may compromise endoscopic evaluation. Recent study by Kim et al⁵ showed that the yield of colonoscopy to identify the source of bleeding in CD patients presenting with acute severe lower GI bleeding was only 11.1%, which was markedly lower than 60% of Belaiche et al's study.¹² Also, our study demonstrated that ileal branch was the most frequent site of active bleeding on angiography in patients with CD ($n = 7$, 53.8%) while jejunum and ileum are not accessible via either colonoscopy or esophagogastroduodenoscopy. Moreover, the exact bleeding site may not be visible during endoscopy in massive bleeding and angiography may prove useful. Additionally, angiography was a preferred choice of investigation in case of postoperative bleeding ($n = 3$).

Among clinical factors, heart rate was the only measurement that responded significantly following angiography with or without TAE. The heart rate decreased significantly after angiography even when angiography did not show evidence of bleeding and a therapeutic attempt was not made. This may be an incidental finding due to intermittent nature of bleeding or intravenous fluid therapy the patients received. Heart rate prior to angiography was higher in the TAE group indicating that the patients with evidence of bleeding on angiography was clinically less stable but the difference was not statistically significant between angiography only group and TAE group. Both systolic and diastolic blood pressure as well as laboratory findings such as Hb and coagulation profile showed no differences between angiography only and TAE group.

In our study, among 39 angiographies of patients who presented with CD-related GI bleeding, 66.7% showed negative findings. This was higher than the recent study by Kim et al¹³ who reported that the incidence of a normal angiogram in a patient with acute upper and lower GI bleeding was 52% and this was related to hemodynamic stability and lower GI bleeding. Among patients with negative angiographic findings, surgical management was required in 5 patients, a repeat angiography was performed in 5 cases with 2 successful TAEs, and one endoscopic clipping was performed. The ability of angiography to detect GI bleeding depends on the rate and nature of bleeding. Studies have shown that bleeding at the rate as low as 0.5 mL/min was demon-

strable on screen-film arteriography in a canine model¹⁴ while *in vitro* digital subtraction arteriography is five to nine times more sensitive.¹⁵ Moreover, intermittent nature of bleeding may make it difficult to demonstrate the bleeding at the time of angiography.

In 13 patients in whom TAE was attempted, TAE achieved 100% technical success rate and 69.2% clinical success rate at 1-month follow-up. These results were comparable to previous published results of TAE in upper GI bleeding with technical success rates of 92% to 100% and clinical success rates of 51% to 94%.^{16–19} In patients with CD, avoiding surgery and minimizing the extent of surgical resection are crucial as patients with CD are likely to undergo more than one operation and multiple surgical resections increase the risk of short bowel syndrome.⁹ While surgical resection remains the standard treatment in patients who are hemodynamically unstable due to CD-related GI bleeding, TAE may be an alternative, effective option of achieving hemostasis while preserving the bowel. There was one case of acute complication of biopsy-proven ischemia related to TAE involving the proximal jejunum and this patient eventually expired 54 days after TAE but due to combined pneumonia rather than TAE-related complication.

Our study has the following limitations. First, this is a retrospective study. Second, the study was performed at a single institution with relatively small number of study population. However, to our knowledge, there has been no study evaluating the role of angiography and TAE in CD-related GI bleeding and acute severe GI bleeding is a rare complication of CD. Third, there are currently no definite guidelines regarding the indication of angiography and TAE in CD-related GI bleeding. Moreover, there are no standardized protocols regarding the embolization techniques including embolization material.

In conclusion, we have demonstrated that angiography is particularly a useful diagnostic tool in patients presenting with CD-related GI bleeding as endoscopy may play a limited role. Although the rate of negative angiographic findings was high (66.7%), TAE showed high technical success rate and acceptable clinical success rate in patients with positive angiographic findings.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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