Transcatheter arterial embolization for massive hemobilia with N-butyl cyanoacrylate (NBCA) Glubran 2

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Abstract

Background

Massive hemobilia is a life-threatening scenario and therapeutic challenge. This study aimed to investigate the efficacy and safety of transcatheter arterial embolization (TAE) using N-butyl cyanoacrylate (NBCA) Glubran 2 for massive hemobilia with arterial injuries.

Methods

From January 2014 to February 2019, 12 patients (mean age, 63.2 ± 12 years) with massive hemobilia were retrospectively evaluated for TAE using NBCA Glubran 2. Patient baseline characteristics, severities of hemobilia, and imaging findings were collected. Emergent TAE was performed using 1:2 – 1:4 mixtures of NBCA and ethiodized oil. Technical success, clinical success, procedure-related complications, and follow-up outcomes were assessed.

Results

Pre-procedure arteriography demonstrated injuries of the right hepatic artery (n = 10), and cystic artery (n = 2). Initial coil embolization distal to the lesions was required in 4 (33.3%) patients to control the high blood flow and prevent end-organ damage. After a mean treatment time of 10.1 ± 5.5 min, technical success was achieved in 100% of the patients without non-target embolization and catheter adhesion. Clinical success was achieved in 11 (91.7%) patients. Major complication was noted in 1 (8.3%) patient with gallbladder necrosis owing to embolization of the cystic artery. During a median follow-up time of 16 months (range, 6 – 36 months), one patient died owing to carcinoma, whereas no patient encountered recurrent hemobilia, embolic material migration or post-embolization complications.

Conclusions

TAE using NBCA Glubran 2 is a rapid, effective, and safe treatment modality for massive hemobilia. This treatment modality may be reserved as a promising alternative option to coil embolization.

Background

Hemobilia is defined as bleeding into the biliary tree and is an uncommon source of upper gastrointestinal bleeding. [1,2] Massive hemobilia with hemodynamic instability is a life-threatening scenario and therapeutic challenge. [3] Although transcatheter arterial embolization (TAE) using coils has become the mainstay treatment for massive hemobilia, [1,2] it might be failed owing to coagulopathy or vascular anatomy complicated by tortuous or narrow feeding arteries. [4,5] N-butyl cyanoacrylate (NBCA) is a liquid permanent embolic material which polymerizes in contact with fluids rich in ions. The

polymerization of NBCA is not depended on coagulation parameters. Thus, it provides better hemostasis than other embolic materials, especially in patients under coagulopathy. [6] Moreover, NBCA offers the advantages of liquid nature and low viscosity for penetrating tortuous and narrow involved arteries. [6] Glubran 2 (GEM, Viareggio, Italy) is a specific surgical glue in which NBCA is combined with another monomer, metacryloxysulfolane, to produce a more pliable and stable polymer whose milder exothermic reaction (45°C) results in less inflammation and histotoxicity than Histoacryl or Trufill. [6]

NBCA Glubran 2 has been used for various bleeding conditions. [7,8] However, in the setting of massive hemobilia, only a few cases have been reported. [9-13] Although the reported outcomes are encouraging, the use of NBCA for massive hemobilia has not been well evaluated. The present study was conducted to evaluated the efficacy and safety outcomes of TAE using NBCA Glubran 2 for massive hemobilia.

Methods

Study design

From January 2014 to February 2019, the data of patients with massive hemobilia who underwent TAE using NBCA in a single center were retrospectively reviewed. This study was approved by the Hospital Review Board. Patient baseline characteristics including demographics, comorbidities, manifestations, medications, etiologies, laboratory data on coagulation parameters (international normalized ratio, partial thromboplastin time, platelet count), and imaging findings (upper endoscopy, computed tomography (CT) and arteriography) were collected. Regarding the severity of hemobilia, hemoglobin level, systolic blood pressure, and the number of red blood cells (RBC) units transfused before TAE were obtained. Procedure-related details including arteriographic findings, bleeding sites, vessel(s) embolized, embolic materials used, treatment time, and procedure-related complications were obtained. Technical success, clinical success, post-embolization complications and follow-up outcomes (recurrent hemobilia, embolic material migration or post-embolization complications) were collected to evaluate the efficacy and safety of NBCA embolization for hemobilia. Data were collected using electronic medical records, including review of clinical notes, laboratory values, procedure images, and procedure reports.

Patients and diagnosis of hemobilia

A total of 12 patients were reviewed and analyzed. The mean age was 63.2 ± 12 years (range, 30-79 years), and half of the patients were male. The leading manifestations were melena (50%) and right upper quadrant pain (41.7%). The Quincke's triad (melena and/or hematemesis, right upper quadrant pain and obstructive jaundice) was presented in 3 (25%) patients. The comorbidities, medications, and prior coagulopathy were listed in Table 1. Regarding the severity of hemobilia, RBC units transfused, hemoglobin level, and systolic blood pressure before the TAE procedure were listed in Table 2.

The diagnosis of hemobilia was based on patients' manifestations, recent interventional procedures, and imaging findings. Hemobilia was diagnosed directly in 4 (33.3%) patients with massive bloody output from a percutaneous transhepatic biliary drainage (PTBD) tube (2 patients) or T-tube (2 patients). The

findings of upper endoscopy and CT were listed in Table 2. Finally, all patients (including five arteriographies as primary imaging examination) received arteriography to confirm the diagnosis and to identify the bleeding sites. The etiologies for hemobilia were iatrogenic except one (8.3%) patient with gallbladder stones and acute cholecystitis (Table 3).

Management of hemobilia and TAE techniques

All patients experienced hemodynamic instability and received resuscitation therapy with fluid or blood transfusion before TAE. During the procedure, 9 (75%) patients were still in unstable hemodynamic status. NBCA, rather than coils, was selected as the primary embolic material for the following reasons: (*a*) rapid embolization was required for unstable hemodynamic status, (*b*) difficulty in using coils successfully, (*c*) difficulty to access the target vessel complicated by extremely tortuous or narrow vascular anatomy. The decision to use NBCA was based predominantly on interventional radiologists' judgment and experience.

Celiac and superior mesenteric arteriographies were performed using a 5-F multipurpose catheter to visualize the arterial anatomy and to identify the source of massive hemobilia using the transfemoral approach. Besides, the patency of portal vein was evaluated by the delayed portal vein phase. A 2.8-F microcatheter (Terumo Corp, Tokyo, Japan) was subsequently introduced coaxially with its tip advanced as close to the bleeding site as possible. After flushing the microcatheter with a 5% dextrose solution, NBCA−ethiodized oil (Ethiodized Poppyseed Oil injection; Hengrui Medicine, Jiangsu, China) mixture (ranging from 1:2 − 1:4 ratio) was injected carefully under real-time high-resolution fluoroscopic mapping until it reached the pseudoaneurysm or bleeding site. According to the operators' experience, initial embolization distal to the lesions with pushable 0.018-inch coils (MicroNester Embolization Coil or Hilal Embolization Microcoil; Cook Medical, Bloomington, USA) was performed in some patients to control the high blood flow and prevent end-organ damage. [14] The ratio, volume, and injection rate of the mixture were based on the size, distance, and flow of target vessel. The microcatheter was removed swiftly after the injection to avoid catheter adhesion. Completion celiac and superior mesenteric artery arteriography were performed to confirm the absence of pseudoaneurysm, extravasation, residual bleeding sites, and to evaluated collateral vessels to the embolized hepatic area. Besides, non-target embolization was also assessed by comparing pre-procedure and completion arteriography.

All patients underwent close surveillance for post-embolization complications and potential aggravation of symptoms and signs after the embolization. Intravenous antibiotic targeting biliary microflora was administrated in all patients. Besides, all patients received post-procedure CT to evaluated the embolization efficacy and potential hepatic infarction or embolic material migration.

Definitions and follow-up

Technical success was defined as complete occlusion of the target vessel or absence of pseudoaneurysm and extravasation on completion arteriography. Clinical success was defined as the cessation of bleeding after TAE with no need for repeat embolization, or additional surgery for

hemostasis. Treatment time was defined as the duration from the identification of bleeding sites to the retraction of microcatheter. Major complication was defined as unplanned surgery, permanent adverse sequelae, or prolonged hospitalization. [15]

During the follow-up, CT and/or color Doppler ultrasound and clinical evaluation were performed on an outpatient basis for all patients (including event-free patients) at 1 and 3 months or sooner when clinically indicated. Any instance of recurrent bleeding, hemobilia, embolic material migration, or post-embolization complications was recorded.

Results

Before the TAE procedure, the patency of portal vein was observed in all patients. Arteriography demonstrated pseudoaneurysm and/or extravasation of the hepatic or cystic artery in 11 (91.6%) patients (Table 3). One patient received upsizing the drain to control hemobilia, and the segmental right hepatic artery transection was the only finding in subsequent arteriography while the upsized drain in place. This patient still received NBCA embolization of the segmental right hepatic artery for safety. Bleeding site complicated by a tortuous or narrow feeding artery was identified in 4 (33.3%) patients (Fig. 1). NBCA as the sole embolic material was used in 8 (66.7%) patients. Initial coil embolization with subsequent NBCA embolization was performed in the remaining 4 patients. The mean injected volume of the mixture was 1.2 ± 0.5 ml (range, 0.5-2.0 ml), and the mean treatment time was 10.1 ± 5.5 min (range, 4–20 min). Technical success was achieved in all patients, and clinical success was achieved in 11 (91.7%) patients. No patient required a secondary NBCA embolization during the same treatment session. Of note, a successful NBCA embolization was achieved in a patient who experienced unsuccessful initial coil embolization (Fig. 2). For the 2 patients who underwent embolization of the main right hepatic artery, the opacification of the distal vessel through intrahepatic collaterals was observed on completion arteriography. One patient experienced a notable hemoglobin decrease (3 g/dL) 3 days after NBCA embolization and was considered a clinical failure. Unfortunately, this patient refused to receive further imaging examinations after the hemoglobin decrease.

Post-procedure CT revealed the absence of previously identified pseudoaneurysms and/or contrast extravasations in all patients. Moreover, no patient had imaging evidence of hepatic infarction, abscess, or embolic material migration, whereas gallbladder necrosis was observed in one patient and was considered as a major complication. Subsequent cholecystectomy was required for this patient. Four (33.3%) patients developed post-embolization abdominal pain and symptoms dismissed after conservative treatment. No other procedure-related complication was noted including non-target embolization and catheter adhesion. Two patients died during the hospitalization: one patient died owing to septicemia, and another patient died due to advanced carcinoma. The post-procedure CT and laboratory tests were evaluated carefully and neither of the deaths seemed to have a relationship with massive hemobilia and the TAE procedure.

During a median follow-up time of 16 months (range, 6–36 months), 1-month, 3-month, 6-month, 12-month follow-up data was achieved in 10 (100%), 10 (100%), 9 (90%), and 8 (80%) patients, respectively. One patient died owing to carcinoma 5 months after the TAE procedure, whereas no patient encountered recurrent hemobilia, post-embolization complications, or NBCA migration into the bile duct.

Discussion

The present study found that TAE using NBCA Glubran 2 was associated with rapid embolization, high success rate, and fewer procedure-related complications. The reported success of coil embolization for hemobilia ranges from 75–100%. [3, 16–19] The technical success and clinical success was 100% and 91.7% in the present study, which are comparable to previous studies. No recurrent hemobilia or bleeding was noted during the follow-up, which demonstrated the durability of NBCA embolization.

Surgery and TAE are considered as first-line therapy for hemodynamically unstable hemobilia, whereas surgery intervention is infrequently necessary unless other interventions are failed. [1, 2, 20] In the present study, one patient developed massive hemobilia owing to gallbladder stones and cholecystitis. Although successful hemostasis was achieved after TAE, the patient developed gallbladder necrosis and received subsequent cholecystectomy. Considering the potential risk of gallbladder necrosis secondary to cystic artery embolization [20] and the necessity of removing the inflamed gallbladder [1], initial surgery intervention might be considered in this scenario.

TAE using coils has become the mainstay treatment for massive hemobilia. [1, 2] The patency of portal vein should be confirmed before TAE, as performing hepatic artery embolization in the setting of portal vein occlusion may lead to significant hepatic ischemia. According to available evidence, coil embolization is associated with high success and fewer complications. [3, 16–19] However, there are several limitations to coil embolization. First, catheterization into the target vessel complicated by extremely tortuous or narrow vascular anatomy may be difficult, thus resulting in failed coil embolization. [4] Second, successful coil embolization is depended on normal coagulation parameters, and it may be failed in patients with coagulopathy. [5] These limitations may be overcome by NBCA Glubran 2. The added ethiodized oil can provide radiopacity and help in adjusting the concentration of NBCA in the mixture and its polymerization time, [21] allowing the operator to control the degree of distal vessel penetration. [7] In the present study, the technical success was achieved in all 4 patients with tortuous or narrow feeding arteries. Besides, NBCA polymerizes regardless of the coagulation condition. Thus, it is effective in patients under coagulopathy with up to 100% success. [5, 14, 22] In the present study, all 3 patients under coagulopathy were successfully treated with NBCA embolization. Furthermore, NBCA has the advantage of rapid embolization, which is essential for massive hemobilia with hemodynamic instability. Yonemitsu et al. [22] reported a significantly reduced time of TAE using NBCA compared with microcoils (9 min vs. 37 min, $p < 0.001$). In the present study, a similar treatment time of 10.1 min was achieved. Another potential advantage of NBCA is cost-effective compared with coils. [7] One ml of NBCA Glubran 2 is comparable in cost to a single conventional pushing coil and is sufficient for successful treatment in the majority of cases. [7, 23] Similarly, no more than 1 ml of NBCA was required in the

present study which may have led to less cost. In addition to above, coil embolization requires distal-to-proximal fashion to avoid back bleeding via intrahepatic arterial collaterals [24] which may result in hepatic ischemia and infarction, [19] especially when pseudoaneurysm or extravasation originated from a main artery. However, in this scenario, NBCA embolization may be used both to embolize the pseudoaneurysm and preserve the main artery. [25] Stent graft or flow-diverting stent may also be used to preserve the main arteries. [26, 27] However, these devices usually require more cost and larger delivery system which may cause difficulty in small target vessel placement. As mentioned above, NBCA Glubran 2 has several potential advantages over coils, which includes embolization of tortuous or narrow target vessels, effectiveness under coagulopathy, rapid embolization, cost-effectiveness, and preservation of the involved main artery. Thus, NBCA embolization is a promising treatment modality for massive hemobilia.

Despite the notable advantages compared with coils, the use of NBCA for hemobilia is still limited, perhaps as a result of the technical difficulties of NBCA embolization and fearing of procedure-related complications. [20] The reported complications regarding NBCA include non-target vessel embolization, adhesion, and fracture of microcatheter. [25, 28] However, according to our experience, NBCA embolization can be performed safely after a short learning curve. Moreover, Madhusudhan et al. [25] reported the modified injection technique of repeated low-dose NBCA mixture (0.1 – 0.3 ml) injection flushing and achieved satisfactory results. In the present study, no inadvertent distal embolization, non-target vessel embolization due to backflow, or catheter adhesion was experienced. This may be because all procedures were performed by experienced interventional radiologists, and they were familiar with the characteristics of the NBCA.

There are several limitations to the present study. First, this is a retrospective study with a relatively small case number. Second, the comparison between NBCA Glubran 2 and coils is not available in the present study. Future comparative studies are needed to find the most appropriate embolic material for massive hemobilia. Third, the decision to use NBCA and coils was made at the discretion of interventional radiologists, which may lead to selection bias. Despite the limitations above, to the best of our knowledge, this study is the largest case series regarding TAE using NBCA Glubran 2 for massive hemobilia.

Conclusion

TAE using NBCA Glubran 2 is a rapid, effective, and safe treatment modality for massive hemobilia. This treatment modality may be reserved as a promising alternative option to coil embolization.

Abbreviations

TAE: transcatheter arterial embolization; NBCA: N-butyl cyanoacrylate; CT: computed tomography; RBC: red blood cells; PTBD: percutaneous transhepatic biliary drainage

Declarations

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Tables

Table 1. Patient baseline characteristics

Variable	Value
Mean age, years (range)	63.2 ± 12 (30-79)
Male	6 (50%)
Manifestations	
Hematemesis	4 (33.3%)
Melena	6 (50%)
Jaundice	4 (33.3%)
Right upper quadrant pain	5 (41.7%)
Bleeding from drainage tube	4 (33.3%)
Comorbidity	
Hypertension	4 (33.3%)
Diabetes mellitus	3 (25%)
Cardiovascular diseases	2 (16.7%)
Gallbladder stones	5 (41.7%)
Cholecystitis	2 (16.7%)
Cirrhosis	1 (8.3%)
Active carcinoma	5 (41.7%)
Deep vein thrombosis	1 (8.3%)
Isolated SMA dissection	1 (8.3%)
Medications	
Antiplatelet	3 (25%)
Anticoagulation	1 (8.3%)
Thrombolysis	1 (8.3%)
Prior coagulopathy [a]	3 (25%)

SMA, superior mesenteric artery.

Data were presented with n (%) unless otherwise stated.

[a] Partial thromboplastin time >45 s and/or platelet count <80,000/mm^3 and/or international normalized ratio >1.5.

Table 2. The severity of hemobilia and imaging findings before TAE

Variable	Value
Hemoglobin before TAE (g/dL)	
Mean ± SD	6.9±1.9
Median (range)	7.5 (3.2-9.9)
Systolic blood pressure before TAE (mmHg)	
Mean ± SD	84.3±22.4
Median (range)	87.5 (46-121)
RBC units transfusion before TAE	
Mean ± SD	5.0±5.4
Median (range)	3.0 (0-15.5)
Imaging findings before TAE	
Upper gastrointestinal endoscopy (available in 2 patients)	
Blood in the second part of duodenum	1 (50%)
Computed tomography (available in 7 patients)	
Hematoma in gallbladder fossa	1 (14.3%)
Pseudoaneurysm	6 (85.7%)
Contrast extravasation	2 (28.6%)

TAE, transcatheter arterial embolization.

Table 3. Procedure-related details and clinical outcomes

Patient No.	Etiology	Arteriographic findings	PSA size (mm)	Bleeding sites	Embolized artery	Embolic material	NBCA: ethiodized oil ratio	Volume (ml)	Treatment time (min)	Technical success	Clinical success
1	LC	PSA	12	Segmental RHA	Segmental RHA	NBCA + Coils	1:4	1.5	16	Yes	Yes
2	LC	PSA	16	Main RHA	Main RHA	NBCA + Coils	1:2	2.0	20	Yes	Yes
3	LC	PSA	15	CA	CA	NBCA	1:4	1.2	9	Yes	Yes
4	Surgery for CC	PSA	6	Subsegmental RHA	Subsegmental RHA	NBCA	1:2	0.4	8	Yes	Yes
5	PTBD	PSA	5	Subsegmental RHA	Subsegmental RHA	NBCA	1:3	0.6	5	Yes	Yes
6	Surgery for CC	PSA	8	Main RHA	Main RHA	NBCA + Coils	1:3	1.0	15	Yes	Yes
7	PTBD	PSA	6	Subsegmental RHA	Segmental RHA	NBCA	1:3	1.5	9	Yes	Yes
8	Surgery for CC	PSA	10	Segmental RHA	Segmental RHA	NBCA	1:3	1.0	5	Yes	Yes
9	Gallbladder stones and cholecystitis	PSA + Extravasation	4	CA	CA	NBCA	1:4	0.8	4	Yes	Yes
10	Surgery for CC	PSA	11	Subsegmental RHA	Segmental RHA	NBCA	1:3	1.5	8	Yes	Yes
11	LC	Extravasation	NA	Subsegmental RHA	Subsegmental RHA	NBCA	1:2	0.5	5	Yes	No
12	PTBD	Arterial transection	NA	Segmental RHA	Segmental RHA	NBCA + Coils	1:2	0.9	17	Yes	Yes

LC, laparoscopic cholecystectomy; CC, Cholangiocarcinoma; PTBD, percutaneous transhepatic biliary drainage; PSA, Pseudoaneurysm; NA, not available; RHA, right hepatic artery; CA, cystic artery; NBCA, n-butyl cyanoacrylate.
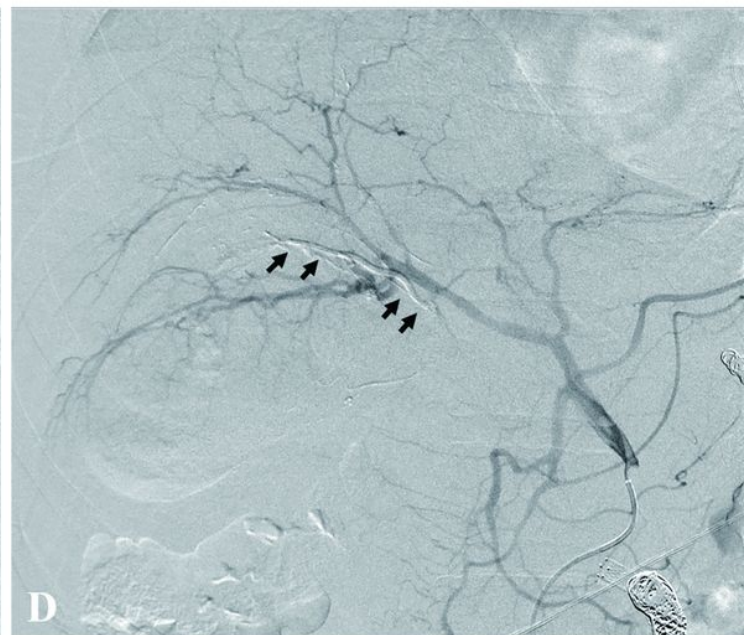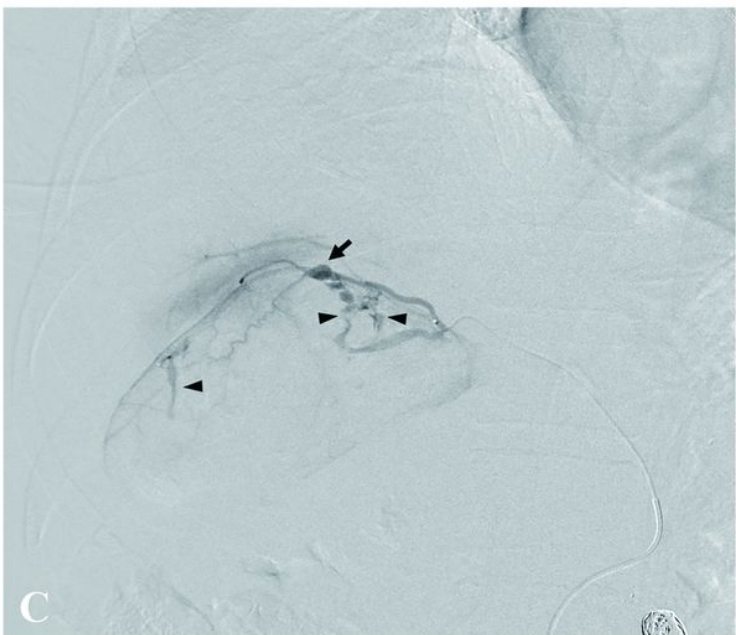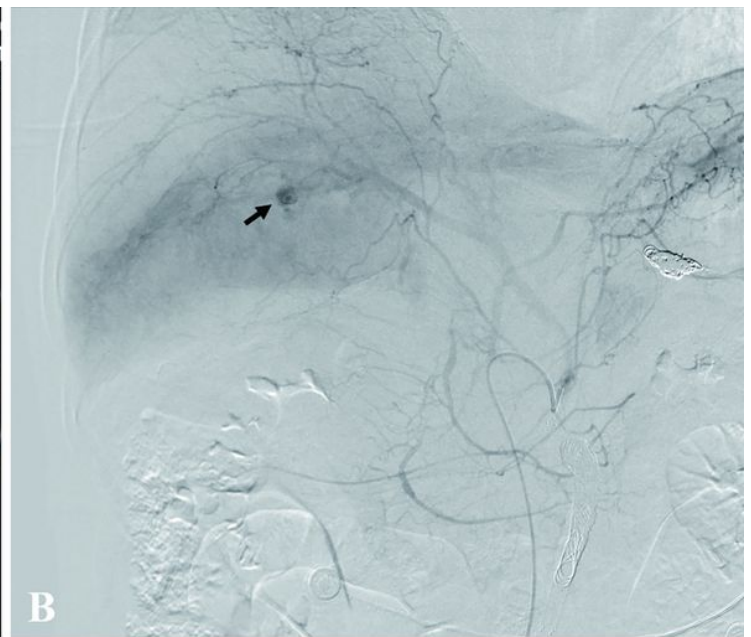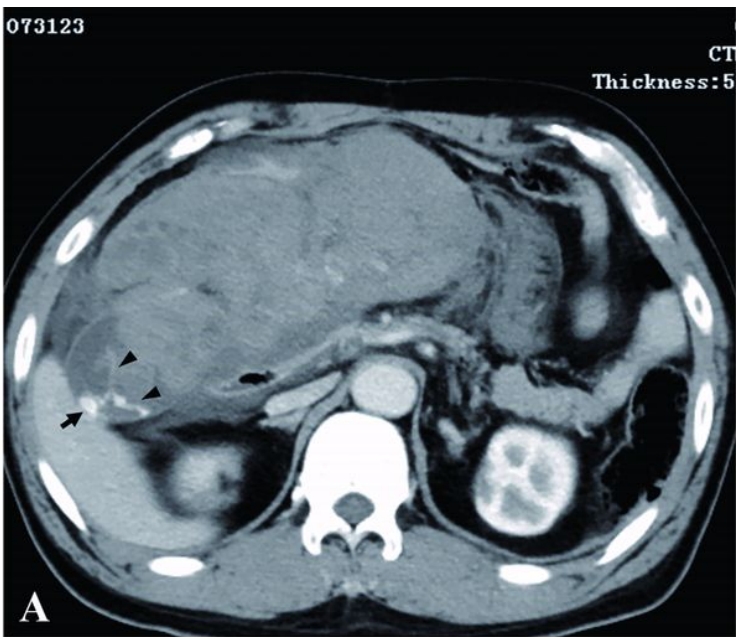
Figures

Figure 1

Successful NBCA embolization for a tortuous and narrow feeding artery. (A) A 58-year-old male developed acute right quadrant pain and melena for 7 hours. The following enhanced abdominal computed tomography revealed a large hematoma originating from the gallbladder fossa, a pseudoaneurysm (arrow) adjacent to the gallbladder, and contrast medium extravasation (arrowhead) into the gallbladder. (B) The routine arteriography of the celiac axis showed a pseudoaneurysm (arrow) originating from the cystic artery. (C) superselective arteriography of the cystic artery showed a pseudoaneurysm (arrow) with multiple extravasations into the gallbladder (arrowhead). (D) A microcoil would have occluded the proximal artery, but not the distal extravasation, which would have led to recurrence; NBCA occluded both. The completion arteriography showed complete occlusion of the cystic artery (arrow).
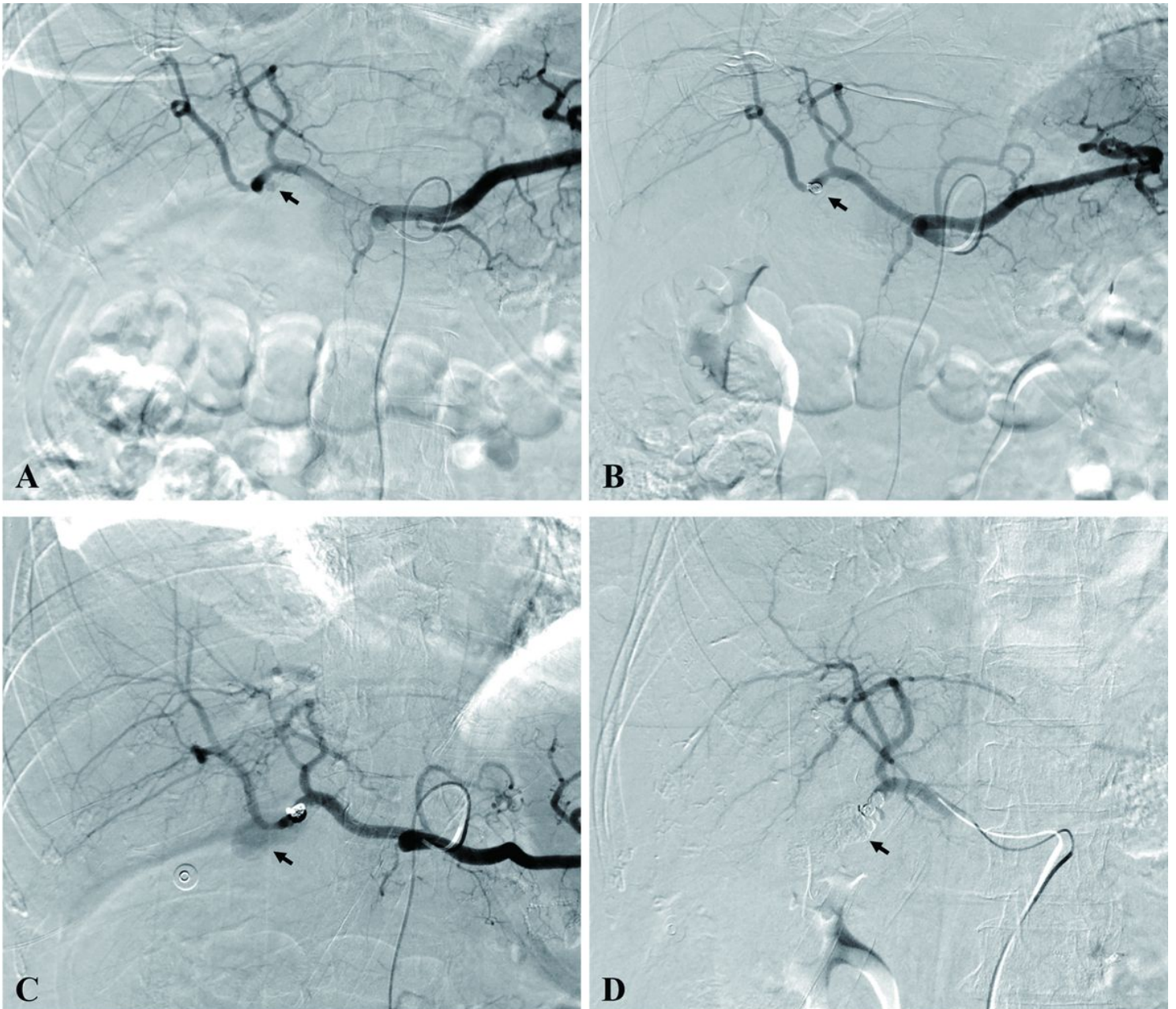
Figure 2

Successful NBCA embolization in a patient with unsuccessful initial coil embolization. (A) A 79-year-old female developed massive hemobilia 7 days after the choledochojejunostomy for cholangiocarcinoma. The arteriography of the celiac axis showed a pseudoaneurysm (arrow) originating from the proximal right hepatic artery. (B) With the need for preservation of the right hepatic artery, the pseudoaneurysm was embolized using microcoils (arrow). Completion arteriography showed the absence of pseudoaneurysm filling. (C) The patient experienced recurrent hemobilia 13 days after the initial embolization and the arteriography showed a large pseudoaneurysm adjacent to the microcoils. (D) The main right hepatic artery was completely embolized with the NBCA mixture and coils. The arrow showed the cast in the pseudoaneurysm.