Early- and intermediate-term outcome of transarterial embolization for symptomatic hepatic focal nodular hyperplasia

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ABSTRACT

Purpose: To evaluate the early- and intermediate-term outcome in patients with symptomatic hepatic focal nodular hyperplasia (FNH) treated with transarterial embolization using bleomycin-iodinated oil and polyvinyl alcohol (PVA) particles.

Materials and methods: In this two-center retrospective study between January 2005 and December 2013, 27 consecutive patients with symptomatic hepatic FNH underwent superselective catheterization by microcatheter techniques and embolization using bleomycin-iodinated oil combined with PVA. Early-term (3–41 months) follow-up of TAE was performed in terms of symptom control, changes in lesion size, and complications. Intermediate-term (45–112 months) follow-up was carried out to assess symptom control and reinterventions for recurrence.

Results: Embolization was performed in 27 patients with 31 lesions. Technical success was achieved in all cases. The follow-up period ranged from three to 112 months. At early-term follow-up, mean lesion diameters were decreased significantly from 6.4 ± 2.7 cm pre-intervention to 3.6 ± 1.8 cm at 3-9 months after embolization (*P<0.001*). A total of 7 lesions had complete resolution during the whole follow-up period. At intermediate-term follow-up, local recurrence was found in 1 treated lesion at 54-months. Contrast-enhanced scans showed complete lack of residual arterial blood supply in the majority of lesions during the follow-up period. There was no major complication associated with the procedure.

Conclusion: Transarterial embolization using bleomycin-iodinated oil and PVA is a feasible, safe and effective alternative in both early- and intermediate-terms for the treatment of symptomatic hepatic FNH.

Keywords: Focal nodular hyperplasia; therapeutic embolization; radiology; interventional; bleomycin

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INTRODUCTION

Focal nodular hyperplasia (FNH) is one of the most common benign hepatic neoplasms with no potential for malignant degeneration. The majority of FNHs are small and asymptomatic. Due to the natural history of FNH with a low risk of hemorrhage or necrosis, patients with asymptomatic definitive FNH may be managed conservatively, and do not require surgical intervention (1, 2).

However, up to a third of FNH patients present with symptoms of abdominal pain or discomfort, which are attributed to the pressure put by the tumor on the liver capsule or surrounding tissues (3). The absolute indications and contraindications for surgery in benign liver disease are highly controversial (4). Indications for surgical excision of hepatic FNH include lesions associated persistent pain or progressive lesions. Surgical excision is the currently applied curative treatment for symptomatic FNH (5); however, it is not always feasible and there are only limited data evaluating the associated risk-benefit balance (6, 7). Previous studies have shown that transarterial embolization (TAE) is an effective alternative to surgical removal in symptomatic hepatic FNH (8-10). Embolic agents commonly used for FNH are ethanol, lipiodol emulsions, polyvinyl alcohol (PVA) particles, gelatin sponge particles and microspheres. Therefore, this retrospective study assessed 27 consecutive patients with symptomatic hepatic FNH who underwent embolization with bleomycin–lipiodol mixture and PVA particles in two centers.

MATERIALS AND METHODS
Ethics statement

This retrospective study was approved by the Institutional Review Board. The procedures of transarterial embolization were explained to each patient, and written informed consent for embolization was obtained from each patient before the procedure.

Study population and pre-procedural evaluation

From January 2005 to December 2013, a total of 27 consecutive patients with symptomatic FNH underwent superselective transarterial embolization. The inclusion criterion for superselective transarterial embolization was proven symptomatic FNH. Exclusion criteria were chronic renal failure and unregulated coagulation parameters. The included patients were 16 men and 11 women aged 18-44 years at admission. Twenty-three patients had a solitary lesion and the remaining four had 2 lesions, for a total of 31 treated lesions. A definitive pathological diagnosis of FNH following percutaneous biopsy was achieved in 22 lesions, and the remaining lesions were considered FNH based on characteristic imaging features. The baseline characteristics of the 27 patients are summarized in Table 1.

Clinical evaluation and imaging examinations with contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI) were performed, and the size (longest axis) of each lesion was measured before and after the procedure.

Table 1. Baseline characteristics of the 27 patients

Characteristics	Value
Age range (y)	18-44
Sex (M:F)	16:11
Number of lesions in a patient	
Solitary lesions	23
Two lesions	4
Lesion diameter (cm)	
Range	3.5-12.9
Mean ±SD	6.4 ± 2.7

Equipment and the embolization technique

Before the procedure, the patients received medications for analgesia and sedation for pain alleviation during embolization.

All patients underwent interventions under local anesthesia via a unilateral femoral approach. Using a 4-Fr Micropuncture System (Cook, Bloomington, US), the right common femoral artery was accessed and a 4-Fr sheath was placed. A 4-Fr hepatic artery catheter (Cordis, USA) was advanced to catheterize the celiac and superior mesenteric arteries. Selective digital subtraction angiography with nonionic contrast agent (Vispaque; GE Healthcare, USA) was performed to evaluate the blood supply to the lesions, and assess the patency of the portal vein.

The lesion-feeding branches were selected, and embolization was performed through a coaxial 2.7- to 3-Fr microcatheter (Progreat; Tokyo, Japan; or Renegade TM, Boston Scientific Corp, USA) under roadmap guidance. The tip of the microcatheter was placed into the targeted artery supplying the lesion, followed by another contrast injection for precise localization and evaluation. Subsequently, a bleomycin-iodinated oil mixture containing 15 mg of bleomycin hydrochloride (Hisun Pfizer, USA) mixed with 15 mL of iodinated oil (Guerbet, Aulnay-sous-Bois, France) was injected through the microcatheter until thick accumulation of the mixture at the lesion periphery. Special care was taken to prevent reflux by injecting the mixture slowly, under continuous fluoroscopic control. The dosage of iodinated oil used varied depending on the lesion size. Then, 300—500μm non-spherical PVA embolic particles (Cook Medical, USA) were injected until nearly complete stasis in the feeding arteries (Fig. 1, 2). When a dual supply to the lesions was suspected, both arterial sources underwent angiographic embolization using microcatheter techniques (Fig. 3). The technical endpoint was to observe stasis of contrast agent in the targeted artery on completion angiography. The technical success of the procedure was defined as the ability to identify and selectively catheterize the arterial supplying the target lesions.

After the procedure, prophylactic antibiotic (1 g of cephazolin, Cefamezin; Pharmacia & Upjohn) treatment was routinely administered intravenously, and appropriate hydration was performed for 2 to 3 days. Analgesics and antiemetics were administered for symptoms occurring immediately post-procedure. The patient's hepatic function, coagulation status and complete blood cell count were evaluated before and after the procedure. Major and minor embolization-related complications were recorded as well.

Patient follow-up

Early-term (3–41 months) follow-up after TAE was performed in terms of symptom control, changes in lesion size, and complications. Then, intermediate-term (45–112 months) follow-up after TAE was carried out to assess symptom control and reinterventions for recurrence.

Initial follow-up imaging and clinical evaluation was carried out in all patients at 3 to 9 months after the procedure. Radiological examination was performed with contrast-enhanced CT or MRI. Therapeutic effects, including changes in lesion size and symptomatic improvement were evaluated after the procedure. The patients were followed-up by radiology and clinical examination post-procedure by two interventional radiologists and a hepatobiliary surgeon. Recurrence was defined as lesion enlargement in the treated area with or without still-enhancing areas within or near the treated area. Imaging data were interpreted by two radiologists with more than 10 years of experience in abdominal imaging.

Statistical analysis

Qualitative data were expressed as number and percentage. Quantitative data are mean±standard deviation (SD), and were compared by Student's t test when appropriate. All statistical analyses were performed with the SPSS 16.0

statistical software (SPSS Inc., Chicago, IL, USA). P<0.05
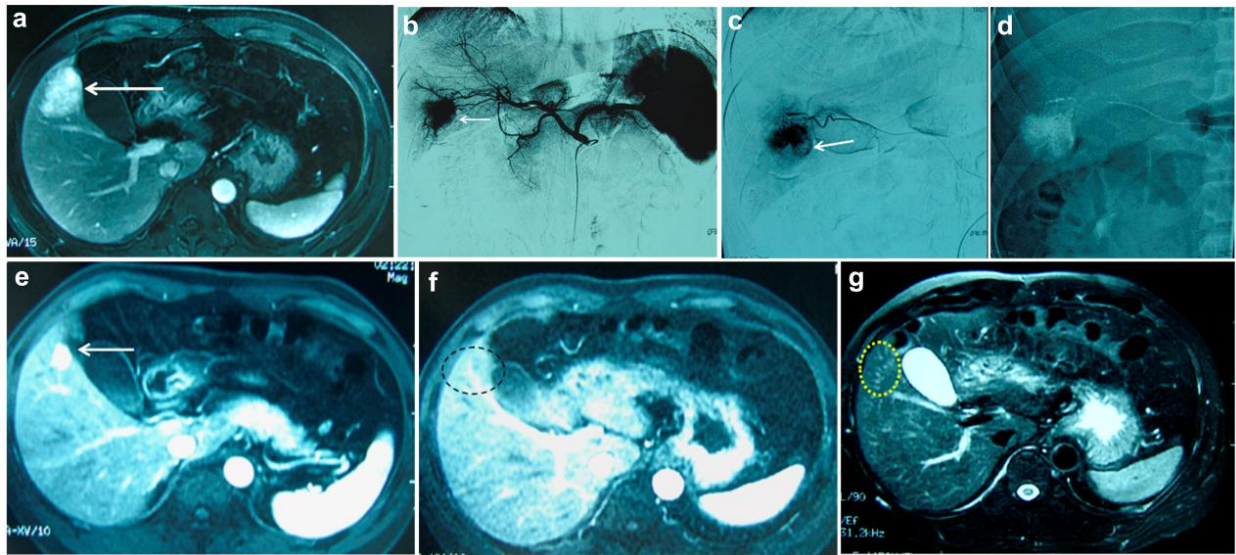was considered statistically significant.

Figure 1. a-g. Images of a 37-year-old male patient suffering from definitive symptomatic FNH. Preprocedural MRI showing a hypervascular mass (arrow) located in segment V on arterial phase contrast-enhanced image (a). Celiac arteriogram (b) revealing a hypervascular lesion (arrow) supplied by branches of the right hepatic artery. Selective angiography of the feeding arterial branch with a microcatheter confirmed the hypervascular mass (arrow) in the late arterial phase (c). Selective embolization (d) of the target artery with a microcatheter. Contrast-enhanced MRI (e) performed at 21-month follow-up demonstrating minimal residual lesion (arrow) at the site of previous embolization. Contrast-enhanced MRI in the arterial phase (f) and T2-weighted MRI (g) obtained at 45-month follow-up, showing no signs of the treated mass at the site of previous embolization (dotted circle), indicating complete resolution of the lesion.
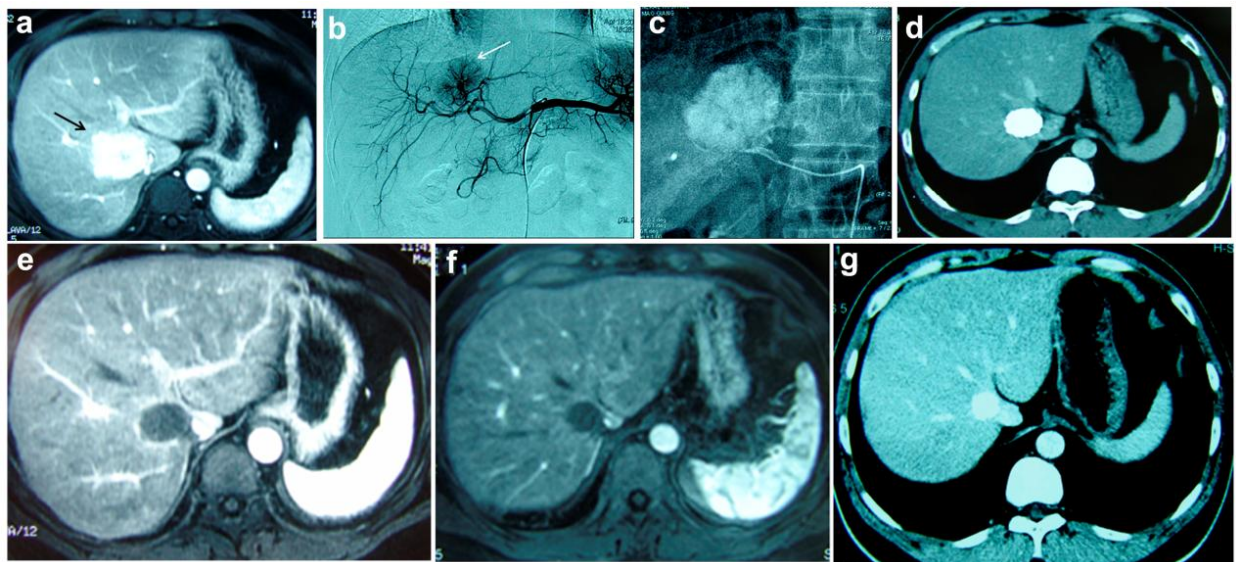

Figure 2. a-g. Images of a 34-year-old male patient suffering from symptomatic FNH. Preprocedural enhanced MRI in the arterial phase (a) showing an enhancing mass (arrow) located in segment VIII. This mass has been enlarged since the previous examination. Celiac arteriogram (b) showing a hypervascular mass (arrow) that was supplied by a dominant feeding artery radiating in a spinning wheel pattern from the mass periphery to the center. (c) The feeding artery was selectively catheterized and embolized with a microcatheter. CT imaging (d) performed at 3-month follow-up showing a significant reduction in lesion size and good uptake of iodized oil by the lesion. Enhanced MRI performed at 6-month (e) and 24-month (f) follow-up, showing no residual enhancement of the mass, which displayed slightly decreased size. Arterial phase CT image (g) obtained at 36-month follow-up demonstrating slight lesion shrinking.
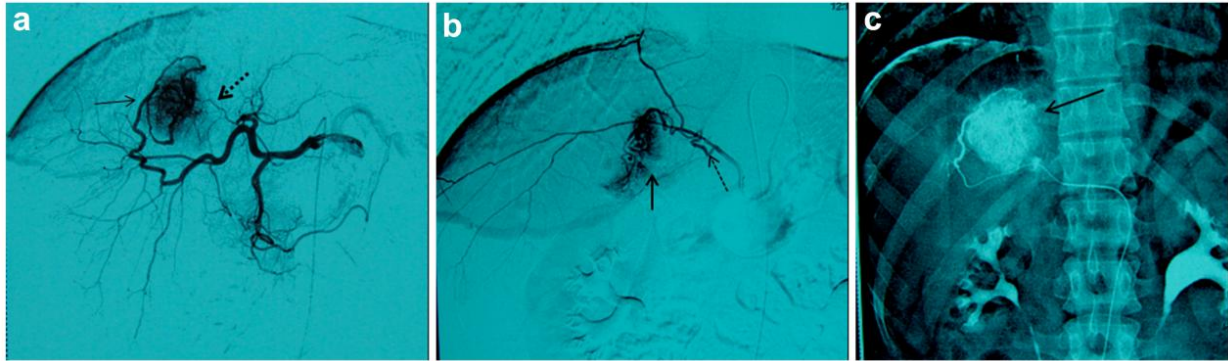
Figure 3. a-c. A 29-year-old female patient suffering from symptomatic FNH of the liver.   Common hepatic arteriogram (a) showing a hypervascular lesion with a dual supply by branches of the right hepatic artery (arrow) and right inferior phrenic artery (dotted arrow). (b) Selective angiography of the right inferior phrenic artery (arrow), confirming collateral (dotted arrow) supply of the hypervascular mass (arrow). (c) Image of selective emboliz ation of the target artery (branch of the right hepatic artery and inferior phrenic artery) with a microcatheter.

RESULTS

All included patients were symptomatic. FNH-associated abdominal or back pain was the most common symptom. Lesion diameters in the 27 patients ranged from 3.5 to 12.9 cm. Embolization was performed for a total 31 lesions, with technical success achieved in all cases. The mean doses of bleomycin used were 10±4 mg per session.

Celiac or hepatic arterial angiography was performed in the majority of cases showing a hypervascular mass with a dominant feeding artery radiating in a spinning wheel pattern from the mass periphery to its center, without arteriovenous shunt or portal vein invasion, which is the characteristic angiographic feature of FNH (Fig. 2b).

Patient follow-up

Follow-up of patients by clinical check-up and radiological imaging with MRI or CT was performed. Early-term follow-up of the 27 patients was performed at 3 to 9 months, and 14 patients were re-evaluated at 12 to 41 months (mean, 27.3±5.9 months) after embolization. Radiological imaging at follow-up demonstrated that lesion diameters significantly decreased from 6.4±2.7 cm before the intervention to 3.6±1.8 cm at early follow-up (Fig. 2; paired t test $P<0.001$). One of the 31 lesions was no longer detectable by MRI at 7-month follow-up, which indicated complete resolution. Post-contrast enhancement images showed complete lack of residual arterial blood supply in most of the other lesions. Initial follow-up CT performed after embolization demonstrated good uptake of iodized oil in most treated lesions, as evaluated by abdominal CT (Fig. 2d).

Fourteen patients were re-evaluated at 12 to 41 months (mean, 27.3 ± 5.9 months). Lesion diameters in the 14 patients decreased from 4.1±1.3 cm at early follow-up to 2.1±1.5 cm, indicating that the treated lesions continued to significantly shrink after the initial follow-up ($P<0.001$).

At intermediate-term follow-up, a total of 11 patients (11/27, 40.7%) were assessed at 45 to 112 months (mean, 66.8±17.2 months). Six of the 13 (6/13, 46.2 %) lesions in these 11 patients had complete resolution at 45-, 48-, 62-, 89-, 107- and 112-month follow-up, respectively (Fig. 1). Another 6 treated lesions (6/13, 46.2 %) were stable with no recurrence or enlargement throughout the observation period. Recurrence was found in 1 of the 13 lesions (1/13, 7.7%). CT examination of the corresponding patient at 54-month follow-up showed arterial enhancing within the treated area on arterial phase imaging and lesion enlargement. The patient presented no recurrence of clinical symptoms. The recurrence was treated with a secondary intervention, and the patient is still followed up. The remaining ten (10/11, 90.9%) patients received no re-interventions during the whole follow-up period.

At early- and intermediate-term follow-up, clinical improvement of abdominal or back pain was found in most cases after embolization. Eighteen patients (18/27, 66.7%) had complete resolution and 9 showed symptom relief after the embolization procedure. All patients showed no recurrence of clinical symptoms throughout the observation period.

Side effects and complications

Hospitalization durations were 5±2 days, and the embolization procedure was well tolerated. Mild pain or ab-dominal discomfort was common during the procedure and remained for 24–48 hours after the embolization procedure. Symptoms of post-embolization syndrome, including nausea, vomiting, pain, and low-grade fever, were not considered complications. These symptoms were transient and self-limited. No major com-plications or adverse events associated with the procedure were noted throughout the follow-up period. Liver function tests showed significantly increased serum transaminase levels at 24 hours after the procedure, which returned to normal values by 3–20 days thereafter in all cases. Bleomycin-related complications, such as sclerosing cholangitis, interstitial pneumonia and pulmonary fibrosis, were not observed postoperatively.

DISCUSSION

Treatment modalities for symptomatic hepatic FNH, including surgical approaches and conservative management, have changed over time and are still evolving. The indications for hepatic resection for the treatment of FNH include persistent pain with a definitive diagnosis and lesions with diagnostic uncertainty (11, 12). Previous studies have reported that surgical resection for symptomatic FNH is an effective treatment with a low incidence of symptom recurrence (13, 14). However, hepatic resection is associated with significant morbidity, and complete excision is usually difficult or even impossible. Postoperative complications related to hepatic resection, including pneumonia, sub-hepatic abscess and wound infection, have been documented (15). Therefore, when surgical treatment is being considered for FNH, the risk-benefit of hepatic resection must be carefully assessed, especially in case of a large or centrally located lesion.

TAE for symptomatic hepatic FNH is considered an effective technique in previous reports. The main indications for embolization include symptomatic lesions, lesion enlargement and refusal of surgical resection (1, 8-10).

In previous studies, technical and clinical successes have been achieved with a variety of embolic agents. Theoretically, bleomycin-iodinated oil and PVA for embolization is more effective than single embolic agents. The mechanism involves the embolic effect of iodinated oil combined with PVA and the sclerosing effect of bleomycin (16). Compared with previous studies, follow-up radiological examinations in the present study scarcely showed residual enhancing FNH tissues after embolization in most cases.

Histologically, the FNH lesion is composed primarily of Kupffer cells and normal hepatocytes, and occurs in response to vascular abnormalities (17). Bleomycin has been used as a sclerosing agent in the treatment of vascular malformation and hemangiomas. Bleomycin helps in the treatment of FNH by exerting a local sclerosing effect on the vascular endothelium, which induces the secondary formation of intraluminal microthrombi and results in the destruction of the feeding arteries of the tumor (18). It should be mentioned that non-hepatic collaterals feeding the lesions also underwent angiographic embolization in the present study, which might also account for the improved results.

Previous studies have indicated that the bleomycin–lipiodol mixture is safe for embolization. Bleomycin doses in the current study were 10±4 mg (range, 5-17 mg), which were much lower than reported toxic levels (cumulative doses of 100–450 mg) (19). Major complications related to bleomycin, such as sclerosing cholangitis and pulmonary fibrosis, were not recorded in the present study.

This study had three limitations. First, due to its retrospective nature, detailed clinical data of the patients pre-embolization were unavailable, and no additional radiological follow-up was performed based on lesion size post-embolization. Secondly, measures of pain reduction to formally evaluate changes in patient's symptoms were absent. Finally, the number of patients assessed and follow-up duration were not uniform or standardized in the present study.

In summary, embolization resulted in improved or even completely resolved symptoms, with significantly decreased lesion size. Transarterial embolization using bleomycin-iodinated oil and PVA may be considered an effective and minimally invasive alternative in both early- and intermediate-terms for the treatment of symptomatic hepatic FNH.

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