

## Original Article

# Interventional embolization in treatment of infantile hepatic hemangiomas

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**Abstract:** Infantile hepatic hemangiomas (IHHs) is the most common hepatic vascular tumor without be developed a standard treatment. We study the digital subtraction angiographic (DSA) characteristics of IHHs, and the effectiveness of transcatheter arterial sclerosing embolization (TASE) alone for its treatment. In this retrospective study, 11 patients treated with TASE were described, consisted of 7 boys and 4 girls, with a mean age of 3.1 months (range 1.5-8.7 months). A successful TASE procedure was performed for every patient. Angiography showed that single hypervascular tumor was supplied by right hepatic artery in 7 patients and left hepatic artery in 1 patient. Hepatic hemangiomas were located in the right lobe in 7 cases, in the left lobe in one case, and in both lobes in 3 cases. Changes in tumor diameter and symptoms were observed. In the months after TASE, tumor size decreased (baseline:  $4.60\pm 2.28$ ; 1 months:  $3.56\pm 1.84$ ; 5 months:  $1.94\pm 1.58$  cm;  $P<0.05$ ), and the patients' condition improved. In summary, these results indicated that TASE was effective and safe for treating giant hepatic hemangioma.

**Keywords:** Infantile hepatic hemangiomas, TASE, embolization, IHHs

## Introduction

Hepatic hemangioma (HH) is the most common, benign tumor, which was previously considered to be a neoplastic lesion originating from the vascular endothelium in infants [1]. Different from adult hepatic hemangiomas, infantile hepatic hemangiomas (IHHs) are present almost exclusively in children before 6 months of age that had completed their growth in utero, and has a slight female preponderance [2, 3]. The failure to recognize the classification of infants hepatic hemangioma led to patients received ineffective and potentially harmful treatment. In 2007, Christisonlagay et al. propose that hepatic hemangiomas could be sorted into 3 group: focal, multifocal, and diffuse based upon their clinical presentation and radiographic appearance [4]. These lesions share the same patterns of growth, histological findings and involution as their cutaneous counterparts: the infantile hemangioma (IH) and the Rapidly Involuting Congenital Hemangioma [5-7].

Historically, the selection of systemic therapies based on the size of the tumor and the symptoms. Giant hepatic hemangiomas are more likely to cause symptoms than their smaller counterparts. Abdominal distention (47.4%), high-output cardiac failure (47.4%), coagulopathy (42.1%), and respiratory distress (31.6%) were the major symptoms [8]. Asymptomatic lesions are usually simply observed. When symptomatic or at risk of rupture, the conventional treatment is surgery. While the risk of surgery is high and the complications are more. With the development of interventional radiology, transcatheter arterial embolization (TAE) has become a possible treatment for hepatic hemangiomas which has been applied to adults and got a better result [9, 10].

The aim of the present study was to assess the therapeutic characteristics and outcomes of infant hepatic hemangioma treated with transcatheter arterial sclerosing (TASE). The results of the present study could be useful for improving the management of giant hepatic hemangioma and patient outcomes.

**Table 1.** Characteristics of 11 patients with giant hepatic hemangioma

Characteristic	Number
Clinical presentation	
Liver tumor and continuous enlargement	11
Coagulant function abnormality	6
Cardiovascular disease	1
Thyroid dysfunction	4
Vomit	1
Location of liver hemangioma	
Right	7
Left	1
Bilateral	3
Number of hemangioma	
1	8
≥2	1
Fill	2
Concomitant diseases	
Skin Hemangioma	2
Anemia	7
Elevation of Serum AFP Levels	8

## Materials and methods

### Patients

In total, 11 patients diagnosed with giant hepatic hemangioma were treated with transcatheter arterial sclerosing embolization (TASE) between August 2016 and November 2017 at the Department of Interventional & hemangioma in the Qilu Children's Hospital of Shandong University (Table 1). The diagnosis of hemangioma was made based on the medical history (age of onset), clinical presentations and pre-operative ultrasound, spiral computed tomography (CT) or magnetic resonance imaging (MRI). The criteria of treatment by TASE in our center are a hepatic hemangioma with a maximal diameter > 4 cm (irrespective of whether or not there are associated symptoms), or a smaller hepatic hemangioma that is associated with symptoms. Data was collected from patient files, including clinical characteristics, imaging examination, treatment effects and side effects. The inclusion criteria for this study were as follows: i) infants were newly diagnosed with giant hepatic hemangioma (maximum diameter > 4 cm [2, 4]) confirmed by ultrasound, CT or MRI; ii) Any size of the liver hemangioma with symptoms; and iii) they underwent TASE as the sole planned treatment. We think there is no absolute contra-

indication for the treatment of TASE, however, we reject surgical contraindication: with serious symptoms not caused by hepatic hemangioma. The ethics committee of Qilu Children's Hospital of Shandong University approved this study and the parents of all infants provided written informed consent for publication.

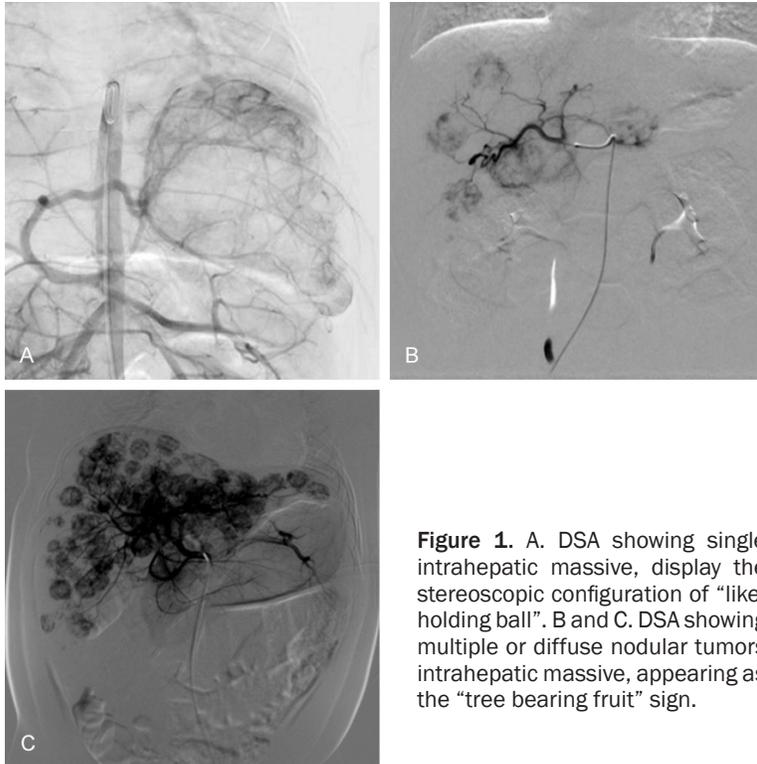
### Treatment protocol

The perineum was disinfected and draped with the patient in the supine position. Under general anesthesia, Seldinger catheterization was performed through the right or left femoral artery. Then the 4 F super Cobra catheter was inserted into the celiac artery through 4 F vascular sheath for Selective Celiac Arteriography, DSA was performed at the same time to determine the location, number, size, staining characteristics and blood supply of the IHH. According to the angiographic findings, the feeding artery of the neoplasm is obviously exposed. Then the 2.6 F micro-catheter was used for superselective catheterization of the feeding artery. After the success, pingyangmycin-lipiodol emulsion (PLE) was injected slowly through the catheter until the periphery of the hemangioma was completely surrounded. Selective Celiac Arteriography performed once again is necessary for judge the degree of embolism of supplying arteries. The polyvinyl alcohol (PVA, 300~500 um) embolization of the feeding artery was performed if the blood supply artery was faster showed by angiography again. The injection was stopped when small branch of portal vein around the tumor was development or the total volume was administered.

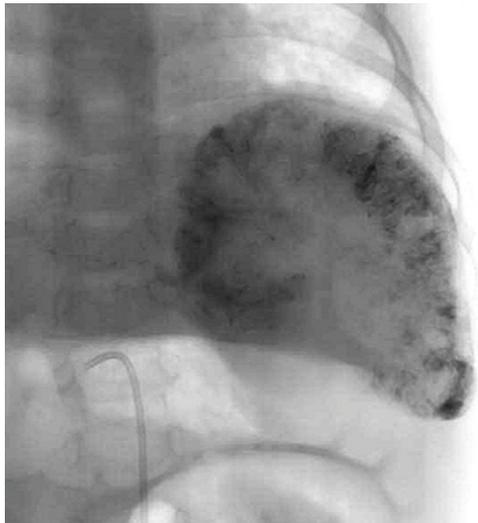
All patients were monitored within 24 hours after the operation include: vital signs, oxygen saturation, routine blood investigations, liver and kidney function and the lower limb skin temperature and color especially. Rehydration and diuresis was considered paramount to protect the liver and prevent infection. In our center, the criterion of rehydration is 1500-2000 ml/m<sup>2</sup> of surface area for three days and blood potassium will be monitor at the same time. Radiation protection in the surgery is necessary especially gonad and thyroid.

Follow-up examinations with CT/MRI were carried out between three weeks and twelve months to observe for changes in tumor size,

## TASE in treatment of IHHs



**Figure 1.** A. DSA showing single intrahepatic massive, display the stereoscopic configuration of “like-holding ball”. B and C. DSA showing multiple or diffuse nodular tumors intrahepatic massive, appearing as the “tree bearing fruit” sign.



**Figure 2.** Fluoroscopy: Lipiodol Filling Shape.

liver function and symptoms (including abdominal pain, fever and complications). Chest photography was taken to observe whether or not pulmonary fibrosis occurred, either before or after embolization.

### *Dosage and preparation of PLE*

It is composed of pingyangmycin, lipiodol, dexamethasone and contrast agents. The dosage of pingyangmycin was 8~12 mg/m<sup>2</sup>, and the con-

centration of lipiodol was 20%~33% (V/V), and the total amount of emulsion was 6~12 ml.

### *Statistical methods*

Statistical analysis was carried out using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for continuous variables (such as hemangioma size and duration of follow-up), and are reported as means ± standard deviations (SD), and evaluated by the Wilcoxon's paired test and the Mann-Whitney U test as appropriate. Differences with *p* values 0.05 were considered to be statistically significant.

### **Results**

#### *Patient characteristics*

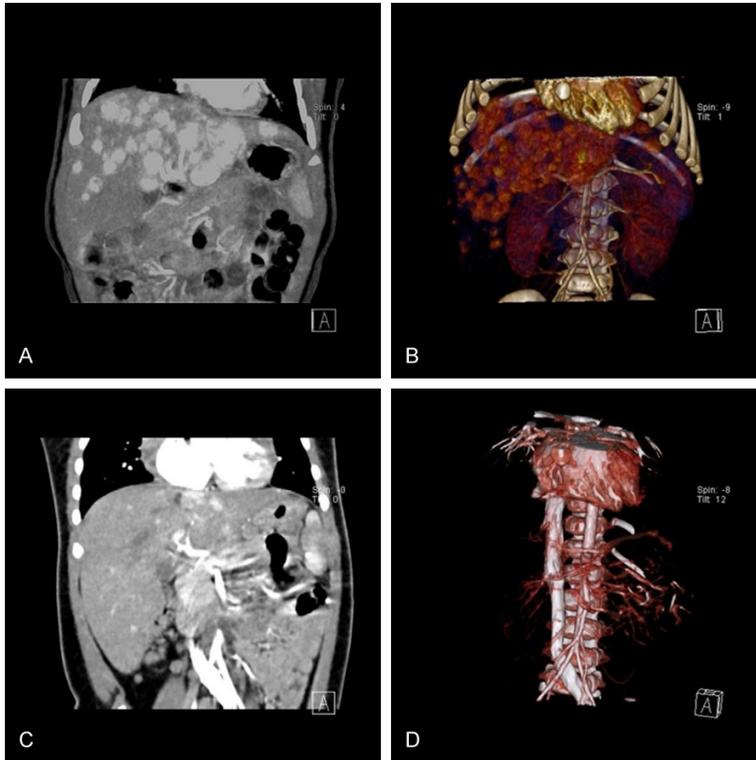
The group consisted of 7 boys and 4 girls, with a mean age of 3.1 months (range 1.58.7 months). Eight patients had a single lesion, 1 had two or more lesions and 2 of them were characterized by diffuse distributed mass in liver. Hepatic hemangiomas were located in the right lobe in 7 cases, in the left lobe in one case, and in both lobes in 3 cases. Of the 11 patients, the hemangiomas had been identified during ultrasonographic views in the fetal screening in the pregnancy; in these patients, tumor volume increased gradually after the baby was born. TASE was indicated on basis of tumor size (> 4 cm). 6 patients have coagulant function abnormality such as thrombopenia. One patient has pulmonary hypertension and right ventricular hypertrophy, 4 patients accompanied by thyroid dysfunction and 1 patient experienced vomit. For the above complications, specific therapeutic regimens were added before the operation; which were alleviated after TASE. Among all the patients in the group, 2 patients had skin hemangiomas were present; 7 suffered from anaemia; and 8 had elevation of serum AFP levels.

#### *Transcatheter arterial sclerosing embolization*

A successful TASE procedure was performed for every patient. Angiography showed that sin-

**Table 2.** Comparison of preoperative and postoperative maximum diameters of infant hepatic hemangiomas in 11 patients

	Preoperative	1 months postoperatively	5 months postoperatively	P
Maximal diameter (cm)	4.60±2.28	3.56±1.84	1.94±1.58	<0.05

**Figure 3.** Female patient before and after TASE: (A, B) diffuse nodule shadowing throughout liver on high resolution computerized tomography before TASE. (C, D) A clear recession of nodules both in size and number after 3 months.

gle hypervascular tumors were supplied by right hepatic artery in 7 patients and left hepatic artery in 1 patient. Under digital subtraction angiography, giant hypervascular tumors display the stereoscopic configuration of “like-holding ball” and multiple popcorn-like blood sinuses in the early arterial phase (**Figure 1A**). Then the intrinsic structure of lesions was demonstrated stain gradually, more blood sinuses were filled by contrast material which will demonstrates stagnation in the delayed image.

In patients with multiple and diffuse hemangiomas, the characteristic of stain gradually from the margin to the center is not pronounced and the lesions were filled by contrast material rapidly. Similar to giant single lesion, delayed image also demonstrates stagnation of con-

trast material. While, unlike multiple hemangiomas, diffuse hemangiomas showed that myriad lesions overlap and interweave in the live arterial phase until that a pooling of contrast material in the lesions filled most of the liver (**Figure 1B, 1C**). Image obtained after injection of hepatic artery of all patients lost the evidence of enhancing nodules or a direct shunt (**Figure 2**).

#### Follow-up

All the children were followed up through the outpatient department for every month (rang: 6-18 months; mean, 10.35±8.77 months) or any time if something happens. Hemangioma size decreased significantly after TASE respectively after one month and 5months ( $P<0.05$ ) (**Table 2, Figure 3**). Liver function was significantly improved the day after TASE (**Table 3**). In

addition, those patients with preoperative clinical symptoms showed a postoperative alleviation of their symptoms that paralleled the decrease in tumor size. Postoperatively, hemorrhage did not occur in any of the patients. Fervescence is a common complication after treatment which occurred in all patients. Loss of appetite caused by liver pain occurs in most cases.

#### Discussion

Infantile hepatic hemangioma (IHH) is the most common hepatic vascular tumor in children. The aim of the present study was to assess the characteristics under DSA and outcomes of three different types of tumors. The negative effect on liver function of embolization was also evaluated by serum total bilirubin, AST and ALT.

**Table 3.** Comparison of preoperative and 1-day postoperative liver function of 26 patients with giant hepatic hemangioma

	ALT (U/L)	AST (U/L)	TB ( $\mu$ mol/L)
Preoperatively	27.0 $\pm$ 16.5	42.0 $\pm$ 9.90	16.8 $\pm$ 13.97
1-day postoperatively	28.4 $\pm$ 18.0	42.8 $\pm$ 16.6	13.7 $\pm$ 13.89
P	0.537	0.810	0.029

In our study, most hepatic hemangiomas were screened by ultrasonography before birth, following with a rapid proliferative phase. To distinguish this from other liver lesions, the further examine must be performed after birth. MRI is the technique of choice in diagnosing infantile hepatic masses. Focal or multifocal centripetal contrast enhancement and dilated feeding and draining vessels on T2-weighted sequences are typical for single and multiple lesions separately [11]. 8 patients were diagnosed with single giant hepatic hemangiomas and 1 patient with multifocal lesions in present study. When the hepatic parenchyma was near-total replacement by the enhancement at MRI, diffuse IHH is likely [12]. DSA of hepatic hemangioma usually can be useful for the differentiation. Angiography of those shows a typical “early leaving but late returning, hanging nut on a twig” sign [10]. While some other hypervascular lesions such as hepatoblastoma in children always show abundant neovascularity and “enhanced quickly, disappeared quickly” sign. And arteriovenous shunting which is often present at the multifocal and diffuse lesions will be discovered by DSA.

The necessity of treatment for hepatic hemangioma is still controversial as its characteristic of initiative recession. According to multivariate analysis of 55 patients, Kassarian et al. [11] consider that congestive heart failure was the only independent predictor of treatment. Similarly, the clinical practice algorithm developed by the Fishman’s group at Boston Children’s Hospital also support that close follow up of infants was should be a top priority for focal hemangioma unless embolization for arteriovenous shunting. Multifocal and diffuse IHHs may require medical intervention and/or therapy because of congestive heart failure (CHF) related those 2 categories was significant risk factors for mortality [13]. We believe that the size must be another indication of intervene treatment with clinical symptoms or not. Indeed, giant haemangiomas have a relevant risk of rupture, particularly when peripherally located and exophytic [14]. Furthermore,

asymptomatic hepatic hemangioma may be accompanied by mild coagulopathy or arteriovenous shunting. Sadly, the identification of the best course of action for patients with IHHs has proven even more vexing. Traditional aggressive treatment such as exaeresis may improve mortality [13]. A minimally invasive approach is in urgent need. The effectiveness of treatment of IHHs with propranolol has been reported [2, 15, 16]. However, even propranolol is not free from side effects and bad therapeutic compliance as long treatment duration (rang: 2-22 months) [2].

With the development of interventional radiology, interventional embolization has become a very valid option. While variety of agency was used by different centers, such as polyvinyl alcohol (PVA), coils, lipiodol and pingyangmycin. Based on previous studies and our clinical experience, it is our opinion that the agency needs include pingyangmycin (PY), lipiodol, dexamethasone and contrast agents. In 1983, Philip et al. [17] have reported 2 cases of infantile hepatic hemangioma with polyvinyl alcohol. A few of PVA was used to slow down the velocity of blood flow and stop loss of medicine in our study. PY induced apoptosis of splenic sinus endothelial cells through the caspase-3 activation pathway, and resulted in endothelial cell necrosis and fibroblast hyperplasia [18]. Lipiodol serves to emulsify and embolize tumor microcirculation which has been widely validated in medical practice [19]. Furthermore, lipiodol can facilitate intracellular PY entry and vascular endothelial cell injury and tumor necrosis following thrombus formation and blocking of blood flow. The purpose of dexamethasone was to prevent allergic shock happening threatened by PY (sensibilisinogen). In our study, all patients were treated with PY-lipiodol-dexamethasone mixture.

After interventionthe, the first and most important thing was to decrease the treatment toxicity. The common complications such as nausea, vomiting, abdominal distention, fever, hepatic dysfunction, abnormal embolization and intrahepatic bile duct injury have been reported in adult [10, 20]. We strongly recommend giving around 3-day continuous rehydration therapy. In our study, about half patients (7 cases) have low-grade fever (not exceeding 39.0°C) after surgery and healed with combined treatment (physical hypothermy). Naus-

ea, vomiting and abdominal distention occurred in some patients, and may be stress reacting process. ALT and AST increased after TASE is rare, except in one patient. No serious complications acct.

### Conclusions

In conclusion, interventional embolotherapy is effective in treatment of hepatic hemangioma with fewer traumas and less complications. The successful treatment with TASE therapy is encouraging and deserves further evaluation.

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