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Original Article

Application of a new triple sequential embolization method in treatment of hepatic hemangioma

Liang Wang, Changlin Deng, Jing Li, Xiaobing Huang, Jian Fan, Xiwen Wang, Ping Liang, Nan You, Lu Zheng

Department of Hepatobiliary Surgery, Xinqiao Hospital of Third Military Medical University, Chongqing 400037, China

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Abstract: Background: The treatment of hepatic hemangiomas by current methods has limitations such as various complications, so more effective methods are needed. Objective: The objective of the present investigation was to explore the effect of sequential application of new triple microsphere method on super selective embolization of capillary and small arteries of the patients with hepatic hemangioma. Materials and methods: A novel triple sequential embolization material was prepared. Totally, 68 patients with hepatic hemangioma were divided into triple sequential embolization method group and iodipin embolization group. The demographics, clinical characteristics, diagnosis, surgery, complications and treatment outcomes were analyzed. Results: The treatment effects of the new triple sequential embolization methods were significantly better than that of the single application of iodipin embolization, of which there were 8 cases with markedly effective treatment effects, 26 cases with valid effects and 6 cases without valid effects. The sizes of tumors were examined in reexamination by CT. Furthermore, the numbers and types of side effects in the triple sequential embolization method group were less than those in the iodipin embolization group. Conclusion: A novel triple sequential embolization material was prepared successfully. Treatment of interventional embolization with the material consisting of microspheres and iodipin in hepatic hemangioma is economic, safe, effective and minimally invasive, and surgical operation can be avoided after interventional embolization treatment in most patients with hepatic hemangioma.

Keywords: New triple sequential embolization method, treatment, hepatic hemangioma, microspheres, iodipin

Introduction

Hepatic hemangioma is one of the most common benign tumors of liver [1-5]. The diagnosis of hepatic hemangioma is mostly based on the typical imaging features of hepatic hemangioma [3, 4], and the diagnostic coincidence rate with magnetic resonance imaging (MRI) is high [6]. Hepatic artery angiography has a unique advantage in the diagnosis of hepatic hemangioma. The application of new techniques such as diffusion weighted magnetic resonance imaging (DWI), liver three-dimensional volume rapid scanning (LAVA) and spectral CT can help to improve the diagnosis rate of the disease [7].

Conventional surgical resection is an important treatment method for hepatic hemangioma, but there were various characteristics of large trauma, many postoperative complications, slow recovery and high cost [8-10]. Interventional therapy is one of effective methods in the treatment of hepatic hemangioma at present. Sclerosants such as absolute ethyl alcohol and sodium morrhuate and iodipin is mixed and injected in the treatment of hepatic hemangioma [11]. Unfortunately, the efficacy of the conventional intervention in some cases is poor and various complications including severe postoperative pain, and even emergence of serious complications of hepatapostema and necrosis and stenosis of bile ducts are caused [12, 13]. Specifically, hardening agent stimulates vessels and may activate platelets, thus formation of thrombus. Therefore, more effective treatment methods without or little side effects are badly needed in clinical applications [14-16].

Drug treatment especially Pingyang mycin also is an important treatment method of hepatic hemangioma. There was case report on bevaci-

zumab in hepatic hemangioma [17]. The preoperative diagnosis revealed that colon cancer was accompanied with hepatic metastasis. In addition, there were various side effects for treatment with drugs on the patients with hepatic hemangioma. However, there was little report on the combination treatment of interventional therapy and drugs.

New biological embolic microsphere material composed of three acrylic polymer coated with biological coating and hydrophilic coating appeared in the markets of China in 2008 domestic, which is suitable for the embolization treatment of arteriovenous malformations and tumors wiht abundant blood supply [18]. Therefore, a new type triple embolic material composed of biological microspheres (embospheres) and Pingyang mycin and super liquid iodipin was investigated in the present study]. We anticipate that the new triple embolic material might have the following advantages: First of all, the diameter of the biological microsphere is 300-500 μm, which is a permanent peripheral embolization agent and it can effectively embolized peripheral artery. The embolization may be more thorough and the time of duration is long, and the tumors shrink quickly, which can effectively avoid formation of collateral circulation resulted from the embolization of hepatic artery. Secondly, Pingyang mycin is a mild sclerotherapy, and its damage effect on vascular endothelial cells is slow, and there is no immediate severe irritation, and the tolerance of patients is good, and combination with iodipin can play superposition roles. Using iodipin combined with Pingyang mycin can embolize capillary in hepatic hemangioma, and the subsequent application of microspheres to embolize arterioles in tumors also play superposition roles. After occlusion of arteriola, the deposition of iodipin in capillary will be enhanced and the curative effect of intervention will be improved.

The objective of the present investigation was to explore the effect of sequential application of new triple microsphere materials on super selective embolization of capillary and small arteries of the patients with hepatic hemangioma. The results demonstrated that the treatment effects were good and side effects were little.

Materials and methods

Drugs and reagents

Lidocaine, Pingyang mycin and iodipin were purchased from Standard departments as described previously [6]. Other reagents were bought from sigma.

Patients

A total of 68 patients with hepatic hemangioma were collected in Xinqiao Hospital of Third Military Medical University between 2010 and 2013. The inclusion and exclusion criteria were as described previously [8]. For the experiments involving human patientss, approval was obtained from the institutional review board of Xinqiao Hospital of Third Military Medical University. Informed consent was provided according to the Declaration of Helsinki. The patients primarily diagnosed of hepatic hemangioma received surgical evaluation, who were identified from the database of the prospective liver and gall of the surgical department. The information of the patients including general characteristics of genders, symptoms, ages, and liver function indexes, and blood routine indexes were collected. The patients were all diagnosed by combined CT scanning, angiography and ultrasonography and pathological examinations. At the same time, the sizes and locations of hemangiomas were observed and recorded [8]. Patients are in line with “the tumor diameter greater than 5 cm, or they have symptoms, or they have strong treatment willingness”

Clinical data of patients with hepatic hemangioma

For experiments involving human subjects, approval was obtained from the institutional review board of Xinqiao Hospital of Third Military Medical University. Informed consent was provided according to the Declaration of Helsinki as previously described [8]. The inclusion and exclusion criteria of the patients with hepatic hemangioma were as described previously [16].

The present clinical investigation had 68 patients including 23 male cases and 45 female cases with ages ranging from 28 to 59

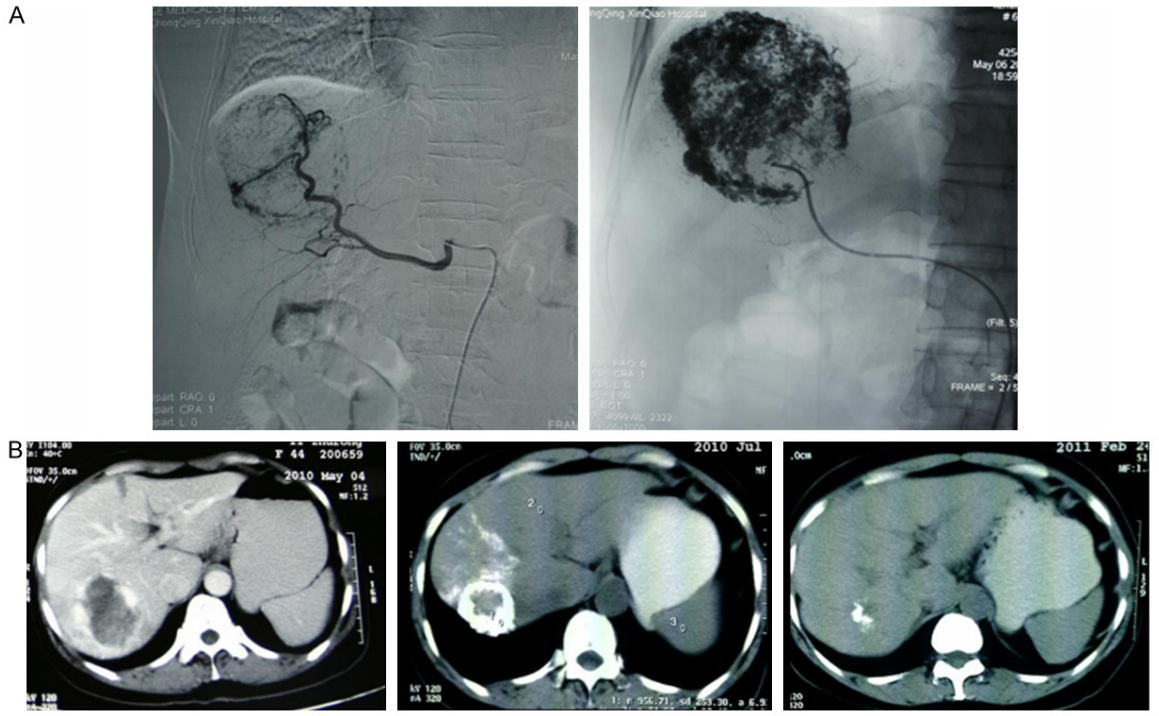

Figure 1. A. Intraoperative angiography (left) and angiogram after operative embolization (right) of female patient 1 with age of 44 years. B. CT results of female patient 1 with age of 44 years. Left: Before embolization treatment (8 × 7 cm). Middle: Three months after treatment of embolization (3 × 3 cm). Right: Nine months after treatment of embolization (2 × 1.5 cm). Postoperative abdominal CT of patient 1 was conducted 3 months and 9 months after operation. The results illustrated that the lesion was significantly reduced, and the liver function was completely normal.

years and an average age of 41 years old. Physical examinations displayed that 21 cases of patients had no significant symptoms and 47 cases of patients exhibited various clinical symptoms especially epigastric discomfort, swelling pain, nausea and vomiting. All the cases were confirmed by B ultrasound, CT plain and enhanced scanning to diagnose. In respect to sites of tumors, there were 35 cases with lobi hepatis dexter and 20 cases with left lobe of liver and 13 cases with both sides. The size was between 5.5 cm × 4.6 cm and 13.6 cm × 12.7 cm. There were 42 patients with single lesion and 26 cases with multiple lesions. There were 68 cases of negative AFP and CHILD Grade A of liver function.

Interventional embolization methods

Femoral artery puncture cannulation and indwelling catheter was conducted by using the modified Seldinger technique. Arteriography was carried out on selective coeliac trunk artery, arteriae hepatica propria and mesenterium with 5 F or 4 F catheter to comprehensively understanding morphology of hepatic artery, blood supply of tumor, location, size and number. Super selective cannula arrived to lesion artery. Because tumor vessel was tiny or tortuous and ordinary catheter was difficult to be used in super selection, 3 F SP micro-catheter cannula was employed. After confirming that the head of catheter was correct, 2-5 ml 1% lidocaine could be injected to prevent angiospasm and pain. The mixture ratio of Pingyang mycin and super liquefaction iodipin was 8 mg:10 ml. Pingyang mycin lipiodol emulsion was slowly injected under low pressure. The injection amount was determined according to specific focus. In the present investigation, dosage of Pingyang mycin lipiodol was about 4-16 mg, and the volume of iodipin was about 5-20 ml to make sure that sinusoid was almost completely filled. After withdraw of micro catheter, 1-5 ml new type vascular embolization agent embosphere was injected. A few minutes later, DSA angiography examination was carried out to understand the effect of embolization. If

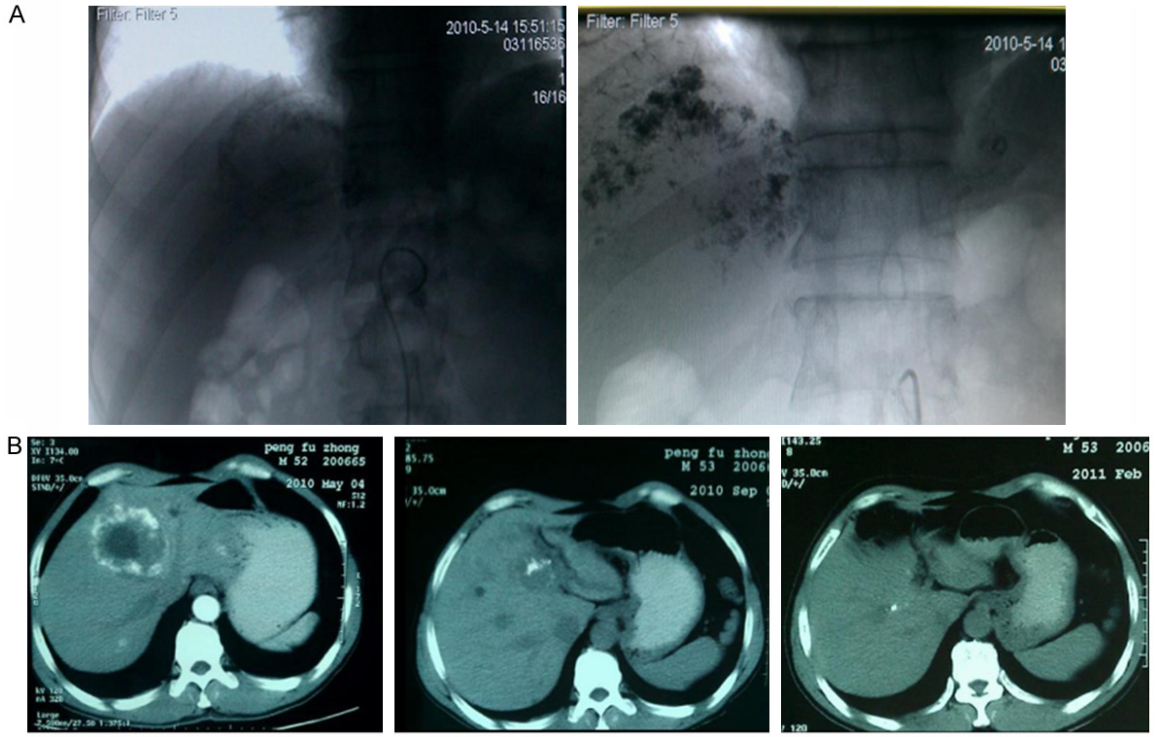

Figure 2. A. Intraoperative angiography (left) and angiogram after operative embolization (right) of male patient 2 with age of 53 years. B. CT results of male patient 2 with age of 53 years. Left: Before embolization treatment (6.5 × 5.5 cm). Middle: Four months after treatment of embolization (3 × 2 cm). Right: Ten months after treatment of embolization (o.5 × 0.5 cm). Postoperative abdominal CT of patient 2 was conducted 4 months and 10 months after operation. The results revealed that the lesion was significantly decreased, abdominal symptoms were significantly relieved, and the liver function was completely normal.

there was no significant contrast medium in tumor blood sinus or feeding artery was basically occluded, embolism could be stopped.

Statistical method

Experimental data were expressed as mean ± standard deviation (x ± s). Mean comparisons were compared with one-way analysis of variance (ANOVA), and t-test was used in multiple comparisons between groups. A *P* less than 0.05 indicated that the difference was statistically significant. A *P* less than 0.01 indicated that the difference was extremely and statistically significant.

Results

Patients

The present clinical investigation had 68 patients including 23 male cases and 45 female cases with ages ranging from 28 to 59 years and an average age of 41 years old. Physical examinations displayed that 21 cases of patients had no significant symptoms and 47 cases of patients exhibited various clinical symptoms especially epigastric discomfort, swelling pain, nausea and vomiting. All the cases were confirmed by B ultrasound, CT plain and enhanced scanning to diagnose. In respect to sites of tumors, there were 35 cases with lobi hepatis dexter and 20 cases with left lobe of liver and 13 cases with both sides. The size was between 5.5 cm × 4.6 cm and 13.6 cm × 12.7 cm. There were 42 patients with single lesion and 26 cases with multiple lesions. There were 68 cases of negative AFP and CHILD Grade A of liver function.

Evaluation of curative effect

In respect to efficacy, there were 30 cases with markedly effective treatment effects, 36 cases with valid effects and 2 cases without valid effects. After follow-up of 3-24 months, the results revealed that the treatment effects of

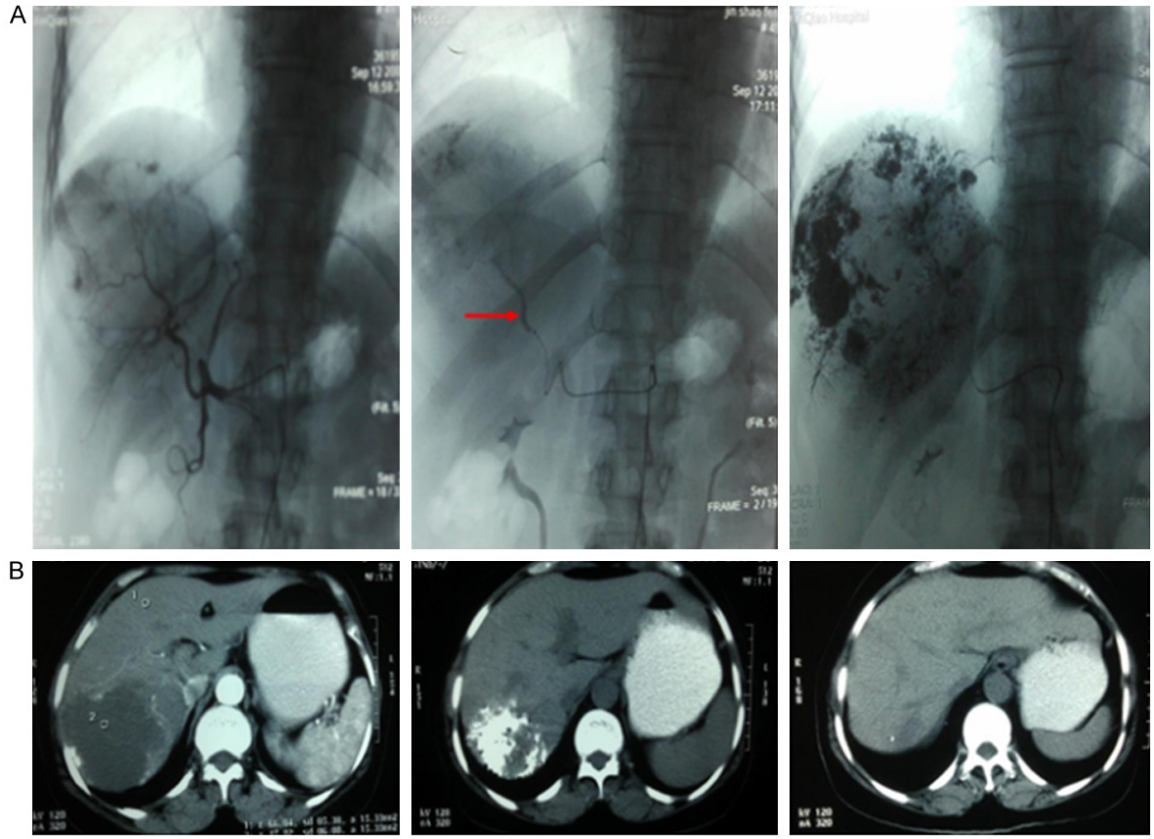

Figure 3. A. Intraoperative angiography (left), Super selective catheterization (micro catheter) (middle) and angiogram after operative embolization (right) of female patient 3 with age of 55 years. B. CT results of female patient 3 with age of 55 years. Left: Before embolization treatment (10 × 8 cm). Middle: Three months after treatment of embolization (7 × 6 cm). Right: Twenty-four months after treatment of embolization, the lesion was disappeared. Postoperative abdominal CT of patient 3 was conducted 3 months after operation. The results revealed that the lesion was significantly reduced, and the second time of embolization was carried out. Twenty-four months after treatment, the lesion was basically disappeared.

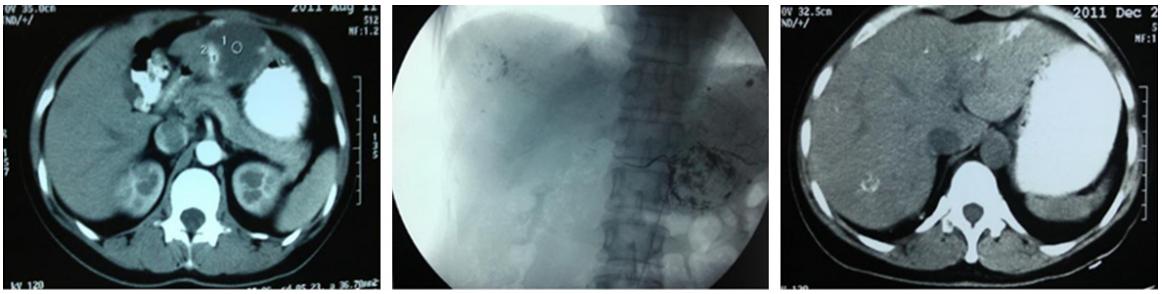

Figure 4. Preoperative CT (left), intraoperative photograph of interventional embolization (middle) and postoperative embolization CT in 3 months (right) of female patient 4 of multiple hepatic hemangioma with age of 44 years.

the new triple sequential embolization methods were significantly better than that of the single application of iodipin embolization, of which there were 40 cases in the routine iodipin embolization group, and there were 8 cases with markedly effective treatment effects, 26 cases with valid effects and 6 cases without valid effects. The sizes of tumors were examined in reexamination by CT. In the present investigation, markedly effective efficacy was defined as the reduced tumor size of hemangioma > 50%, and effective efficacy was defined as the reduced tumor size of hemangioma was about 30%-50%, and invalid efficacy was

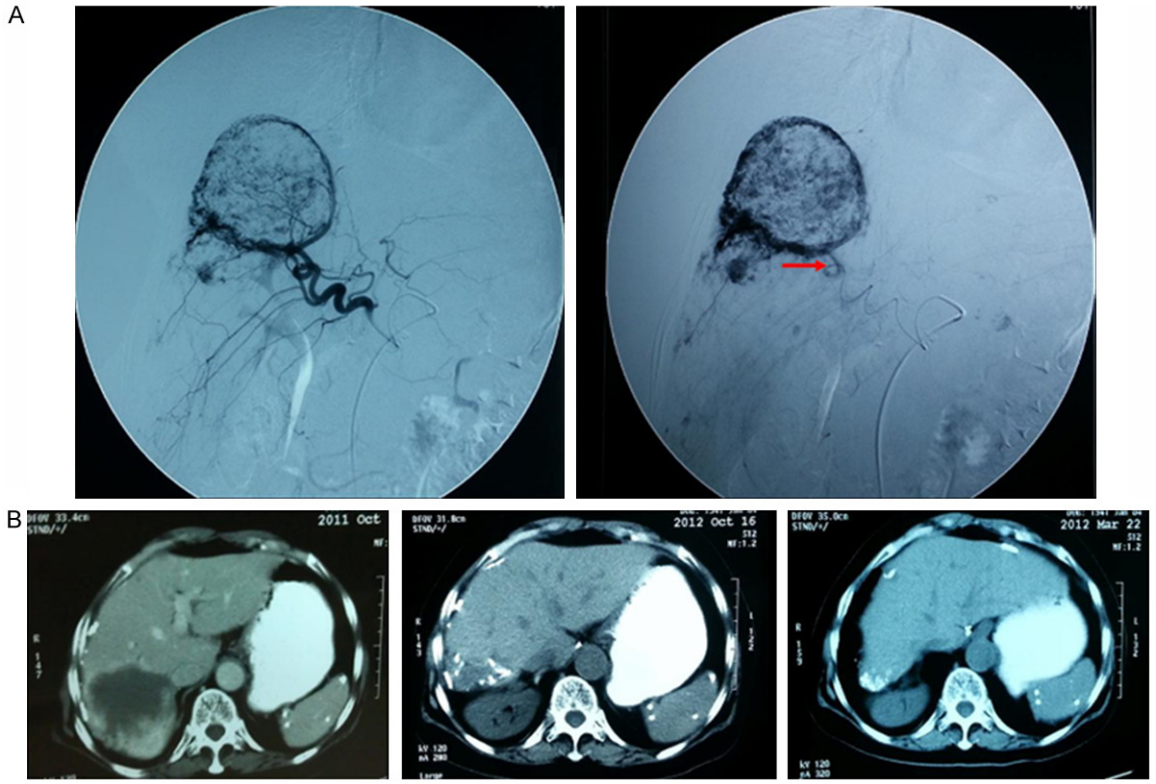

Figure 5. A. Intraoperative angiography (left) and radiography after embolization (micro catheter) (right) of female patient 5 with age of 70 years. B. CT results of female patient 5 with age of 70 years. Left: Before embolization treatment (10 × 9 cm). Middle: Two months after treatment of embolization (4 × 2.5 cm). Right: Five months after treatment of embolization of the lesion of 2.5 × 2 cm. Postoperative abdominal CT of patient 5 was conducted 2 months after operation. The results showed that the lesion was significantly reduced, and 5 months after operation, lesions continued to shrink in one more time of test, and the original abdominal distension symptoms were disappeared.

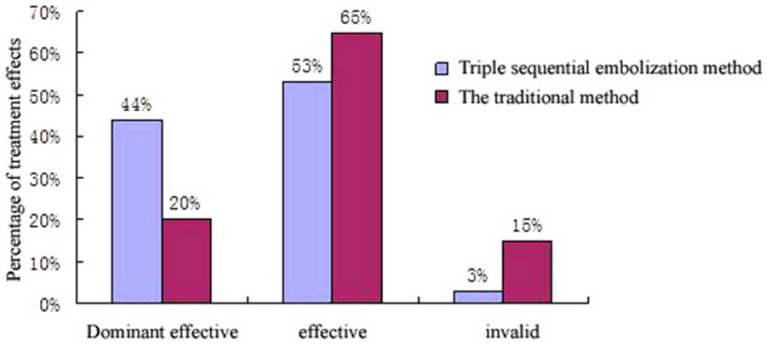

Figure 6. Outcomes of the patients with different treatment methods. The patients were treated with the triple sequential embolization method and the traditional method, and the percentage of treatment effects was shown.

defined as the reduced tumor size of hemangioma < 30%.

In improvement of symptoms and complications, 68 cases of patients in our department demonstrated improved preoperative symptoms of abdominal distension, abdominal pain, back pain and nausea and vomiting after operation, and the main complications included liver pain and fever. The incidence rate of the new triple sequential embolization method was lower than that of the conventional scheme, and the present method could be easily controlled without serious complications. The treatment effects of the new triple sequential embolization methods were significantly better than that of the single application of iodipin embolization, of which there were 8 cases with markedly effective treatment effects, 26 cases with valid effects and 6 cases without valid effects (**Figure 6**).

Outcomes of the 5 patients

Patients are in line with "the tumor diameter greater than 5 cm, or they have symptoms, or

Table 1. Comparisons between Triple sequential embolization and traditional method

Items	Demographics	Clinical characteristics	Diagnosis	Surgery	Complications	Treatment outcomes
Triple sequential embolization	Same	Same	Easy	Easy	None or less	Better
Traditional method	Same	Same	Easy	Difficult	More	Good

they have strong treatment willingness". Various catheters (left) and microspheres (right) employed in the present investigation were. A total of 5 typical patients named as patient 1, 2, 3, 4 and 5 were diagnosed and treated in the current investigation and the results were as follows:

Intraoperative angiography (left) and angiogram after operative embolization (right) of female patient 1 with age of 44 years was as depicted in **Figure 1A**. As demonstrated in **Figure 1B**, CT results of female patient 1 with age of 44 years showed the sizes of lesions: before embolization treatment, the size of lesion was 8 × 7 cm. Three months after treatment of embolization, the size of lesion was 3 × 3 cm. Nine months after treatment of embolization, the size of lesion was 2 × 1.5 cm. Postoperative abdominal CT of patient 1 was conducted 3 months and 9 months after operation. The results illustrated that the lesion was significantly reduced, and the liver function was completely normal.

Intraoperative angiography (left) and angiogram after operative embolization (right) of male patient 2 with age of 53 years was shown in **Figure 2A**. CT results of male patient 2 with age of 53 years were in **Figure 2B**. Before embolization treatment, the size of lesion was 6.5 × 5.5 cm. Four months after treatment of embolization, the size of lesion was 3 × 2 cm. Ten months after treatment of embolization, the size of lesion was 0.5 × 0.5 cm. Postoperative abdominal CT of patient 2 was conducted 4 months and 10 months after operation. The results revealed that the lesion was significantly decreased, abdominal symptoms were significantly relieved, and the liver function was completely normal.

Intraoperative angiography (left), Super selective catheterization (micro catheter) (middle) and angiogram after operative embolization (right) of female patient 3 with age of 55 years was demonstrated in **Figure 3A**. CT results of female patient 3 with age of 55 years were illustrated in **Figure 3B**. Before embolization treatment, the size of lesion was 10 × 8 cm. Three months after treatment of embolization, the size of lesion was 7 × 6 cm. Twenty-four months after treatment of embolization, the lesion was disappeared. Postoperative abdominal CT of patient 3 was conducted 3 months after operation. The results revealed that the lesion was significantly reduced, and the second time of embolization was carried out. Twenty-four months after treatment, the lesion was basically disappeared.

Preoperative CT (left), intraoperative photograph of interventional embolization (middle) and postoperative embolization CT in 3 months (right) of female patient 4 of multiple hepatic hemangioma with age of 44 years was illustrated in **Figure 4**.

Intraoperative angiography (left) and radiography after embolization (micro catheter) (right) of female patient 5 with age of 70 years was shown in **Figure 5A**. **Figure 5B** displayed the CT results of female patient 5 with age of 70 years. Before embolization treatment, the size of lesion was 10 × 9 cm. Two months after treatment of embolization, the size of lesion was 4 × 2.5 cm. Five months after treatment of embolization, the size of lesion was 2.5 × 2 cm. Postoperative abdominal CT of patient 5 was conducted 2 months after operation. The results showed that the lesion was significantly reduced, and 5 months after operation, lesions continued to shrink in one more time of test, and the original abdominal distension symptoms were disappeared.

Complications

The main complications were hematoma at puncture sites, fever, abnormal liver function and liver pain etc.

Discussion

Hepatic hemangioma is one the most common tumors of livers with tumor sizes of millimeters

to in diffusion of the whole liver [1-3]. The lesions of the patients with hepatic hemangiomas are asymptomatic in general, leading to various complications both in children and adults [4-7]. The complications in children are mainly congestive heart failures and hepatomegaly, while the adult patients with hepatic hemangiomas are generally involved in jaundice, discomfort or pain of right upper quadrant and other symptoms [8]. Although hepatic hemangiomas severely threaten people's life and health, the treatment effects of current methods are not good enough and there are various complications. Thus, more effective methods are badly needed.

The most important finding in the present investigation is that the novel microsphere materials combined with iodipin play synergistic reactions in the treatment of the patients with hepatic hemangioma, and satisfactory effects are achieved and there is limited complications in most patients (**Table 1**). After embolization of small arteries with microspheres, the blood pressure in the capillaries is low, and better effects of lipiodol deposition are achieved, so all the 68 patients obtained overall satisfaction efficacies. Secondly, the treatment method has high stability. The technical procedures are stable and reliable, and most patients showed similar and effective treatment effects. The treatment scheme of Pingyang mycin combined with iodipin in hepatic hemangioma is safe and effective, and sequential application of new materials such as microsphere for embolism can improve the curative effect while the complications are not increased. Intraoperative application of super selective arterial intubation can effectively prevent ectopic embolism. Doses of emboliaztion agents can be reasonably controlled according to tumor size, blood supply, position and reflux condition. In view of the huge multiple hepatic hemangioma, gradation and multiple embolism scheme can be applied.

There are several limitations in the present investigation. First of all, only limitated numbers of patients with hepatic hemangioma received better treatment effects and less complications comparing with previous reports. Secondly, the follow-up time is only more than 1 year, and longer observation time will be needed to further validate the findings. Thirdly, the underlying mechanism of the combined application of Pingyang mycin with iodipin remains unknown.

In conclusion, treatment of interventional embolization with a new triple sequential embolization material consisting of microspheres and iodipin in hepatic hemangioma is economic, safe, effective and minimally invasive, and surgical operation can be avoided after interventional embolization treatment in most patients with hepatic hemangioma.

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Disclosure of conflict of interest

None.

Address correspondence to: Lu Zheng, Department of Hepatobiliary Surgery, Xinqiao Hospital of Third Military Medical University, Chongqing 400037, China. Tel: +862368774506; Fax: +862368755606; E-mail: xqyyzl1@163.com

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