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World J Gastroenterol 2004;10(6):825-829
World Journal of Gastroenterology
 ISSN 1007-9327

• LIVER CANCER •

Comparison of long-term effects between intra-arterially delivered ethanol and Gelfoam for the treatment of severe arterioportal shunt in patients with hepatocellular carcinoma

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Received: 2003-11-12 **Accepted:** 2003-12-16

Abstract

AIM: To evaluate long-term effect of ethanol embolization for the treatment of hepatocellular carcinoma (HCC) with severe hepatic arterioportal shunt (APS), compared with Gelfoam embolization.

METHODS: Sixty-four patients (ethanol group) and 33 patients (Gelfoam group) with HCC and APS were respectively treated with ethanol and Gelfoam for APS before the routine interventional treatment for the tumor. Frequency of recanalization of shunt, complete occlusion of the shunt, side effects, complications, and survival rates were analyzed between the two groups.

RESULTS: The occlusion rate of APS after initial treatment in ethanol group was 70.3%(45/64), and recanalization rate of 1 month after embolization was 17.8%(8/45), and complete occlusion rate was 82.8%(53/64). Those in Gelfoam group were 63.6%(21/33), 85.7%(18/21), and 18.2%(6/33). There were significant differences in recanalization rate and complete occlusion rate between the two groups ($P<0.05$). The survival rates in ethanol group were 78% at 6 months, 49% at 12 months, 25% at 24 months, whereas those in Gelfoam group were 58% at 6 months, 23% at 12 months, 15% at 24 months. The ethanol group showed significantly better survival than Gelfoam group ($P<0.05$). In the ethanol group, there was a significant prolongation of survival in patients with monofocal HCC ($P<0.05$) and Child class A ($P<0.05$). There were no significant differences in survival rate in the Gelfoam group with regard to the number of tumor and Child class ($P>0.05$). The incidence rate of abdominal pain during procedure in ethanol group was 82.8%. There was no significant difference in postembolization syndromes between two groups. Procedure-related hepatic failure did not occur in ethanol group.

CONCLUSION: Ethanol embolization for patients with HCC and severe APS is efficacious and safe, and may contribute to prolongation of the life span versus Gelfoam embolization.

Huang MS, Lin Q, Jiang ZB, Zhu KS, Guan SH, Li ZR, Shan H. Comparison of long-term effects between intra-arterially delivered ethanol and Gelfoam for the treatment of severe arterioportal shunt in patients with hepatocellular carcinoma. *World J Gastroenterol* 2004; 10(6): 825-829
http://www.wjgnet.com/1007-9327/10/825.asp

INTRODUCTION

Hepatocellular carcinoma is frequently associated with arterioportal shunts. Kido and Ngan *et al*[1,2] reported that APS in HCC occurred in 60%, and Okuda *et al*[3] reported that severe APS of main or right or left portal veins occurred in 30% of patients with HCC. Severe APS led to life threatening conditions (*e.g.*, esophageal varices, ascites and hepatic encephalopathy) as a result of portal regurgitation or portal hypertension[4-7]. To improve portal hypertension caused by severe APS in patients with HCC, APS needs to be treated. To date, Gelfoam and steel coil are the most commonly used embolic materials[8-10]. However, any long-term effect of embolization of APS with steel coil or Gelfoam on survival have not been proved, although they produced a good short-term effect as reported[8-10]. It has been a hot issue how to choose an ideal embolic material to occlude APS. In this study, we used ethanol as the embolic material to treat the APS before the routine interventional treatment for 64 patients. The purpose of this study was to evaluate the long-term effect of the transcatheter arterial embolization (TAE) of APS with new embolic material in patients with HCC and APS, in comparision with the most commonly used material: Gelfoam.

MATERIALS AND METHODS

Patients

Among 596 patients with HCC treated with transcatheter arterial chemoembolization (TACE) or transcatheter arterial infusion chemotherapy (TAI) at the 3rd Affiliated Hospital of Sun Yat-sen University from February 1999 to March 2003, 161(27%) patients with severe APS were identified by digital subtraction angiography (DSA). We excluded patients with Child class C disease and patients who underwent the treatment of surgical resection, percutaneous local ethanol injection, microwave coagulation, or systemic chemotherapy throughout the study period. According to the exclusive criteria, 64 of 161 patients were excluded from this study. Ninety-seven patients were enrolled in our study (78 men and 19 women, ranging from 21 to 78 years of age; mean age, 57.9). All the patients were treated with TAI or TACE after undergoing embolization of APS.

Written informed consent was obtained from the patients involved in this study. We divided the patients into 2 groups: ethanol group, in which APS was treated with ethanol for 64 patients from April 2000 to March 2003, and Gelfoam group, in which APS was treated with gelatin sponge particles for 33 patients from February 1999 to March 2000. The clinical characteristics of two therapeutic groups were illustrated in Table 1. Although this was a retrospective nonrandomized

study, there were no significant differences between two groups in background factors (Table 1).

Table 1 Clinicopathologic characteristics of patients with HCC and APS

Characteristics	Ethanol group (n=64)	Gelfoam group (n=33)	P value
Age (y)	56.4±21.4	52.3±26.6	0.42
Sex (M/F)	52/12	25/7	0.72
Child classification			
Child class A	35(55%)	20(61%)	
Child class B	29(45%)	13(39%)	0.56
Serum total bilirubin (mg/ml)	1.6±1.5	2.0±1.8	0.31
Serum albumin (g/dl)	3.6±0.8	3.4±1.1	0.30
Number of tumors			
1	15(23%)	11(33%)	
2~3	19(30%)	8(24%)	
⩾4, diffuse	30(47%)	14(43%)	0.32

Treatments

Firstly, arteriography of hepatic common artery was performed to visualize the arterial vascularization of the liver and to identify the location, severity and direction of vessels of APS. Secondly, a 3-F microcatheter was superselectively inserted into the dominant artery of APS through a 5-F catheter. The embolic material was injected to occlude APS. All diagnostic studies and treatments of APS were performed during the same procedure.

Ethanol group: 2-3 mL absolute ethanol was injected slowly and gently at the rate of about 1 mL/min after 2 mL 10g/L lidocaine was injected through catheter. About 5-10 min later, a repeated DSA was performed to evaluate the occlusive extent of APS. If persistence of APS was shown, another 2-3 mL ethanol was injected repeatedly until the occlusion of APS was confirmed with angiography.

Gelfoam group: Gelatin sponge particles (size, 1 mm×1 mm× 1 mm) were mixed with contrast media (Iopamilon, Schering, Berlin, Germany) and were injected with 1-mL tuberculin syringe under fluoroscopic monitoring until a slow flow or stasis of APS was demonstrated. Then arteriography was done again to confirm the occlusion of APS. If APS could not be occluded with Gelatin sponge particles (size, 1 mm×1 mm×1 mm) and microcatheter, a 4F Rösch hepatic catheter or 4F cobra catheter would replace the 3-F microcatheter and be inserted into or by the way of the feeding artery of shunt. Then several large pieces of Gelfoam (beyond 1×1×1 mm) were used to occlude the shunt.

After embolization of APS, the routine interventional therapy was done for the tumor, as reported[11-15]. After catheter was inserted into feeding artery of tumour, pirarubicin (THP)/lipiodol(LPD) emulsion was injected through catheter for the patients without tumour thrombus in main portal vein. THP/LPD was prepared with the following procedure. THP (60-80 mg) was dissolved in 3-10 mL of 50 g/L glucose and then mixed with 3-10 mL LPD at a 1:1 ratio repeating approximately 10 times. Then gelatin sponges embolization of feeding artery was performed. We only injected pirarubicin (60-80 mg) which was dissolved in 100 mL of 50g/L glucose for the patients with tumour thrombus in main portal vein.

Criteria for evaluating embolic effect

Recanalization of APS was defined as APS was shown again at arterial phase of DSA 1 month postprocedure in the patients who had the complete occlusion of shunt after initial treatment. Complete occlusion of APS was defined as APS was not demonstrated in DSA for 2 times consecutively.

Follow-up protocol

All patients were followed up by means of spiral CT scan of liver and laboratory tests such as concentrations of α-fetoprotein, liver function before and after treatment. Change of APS was evaluated with DSA which was performed 1 and 2 mo after initial treatment. Then all patients should be followed up every 2-3 mo. When elevation of tumor markers (α-fetoprotein), persistence of APS or recurrence of tumor were observed, patients were readmitted for angiography and treatment as before.

Statistical analysis

The cumulative proportional survival rates were calculated according to the Kaplan-Meier method. The starting point was defined as the day of initial treatment. The significance of differences between background clinical characteristics of the patients groups (ethanol and Gelfoam) was assessed with the χ^2 test and Student' s t test. The significance of difference in survival rates between patients was evaluated by the generalized Wilcoxon test. Values of $P<0.05$ were considered significant.

RESULTS

Results of occlusion of APS

In the ethanol group, APS was occluded completely at the initial treatment in 45(70.3%) patients. Among them, recanalization of APS 1 month post-procedure was shown in 8(17.8%). There were 30(46.9%) patients with APS 1 month after initial treatment, which included incomplete occlusion of APS in the initial treatment, recanalizational and newly occurred APS. Of them APSs were occluded completely after a second treatment in 16 patients. The rate of complete occlusion of APS in ethanol group was 82.8%(53/64) totally (Figures 1A-F).

In the Gelfoam group, 21(63.6%) patients had the complete occlusion of APS in the initial treatment. Recanalization of APS occurred in 18(85.7%) patients of them 1 mo after initial treatment. Thirty (90.6%) patients were with APS 1 mo after initial treatment, which consisted of incomplete occlusion of APS in the initial treatment, recanalization and newly occurred APS. In 3 patients of them, APS were occluded completely after another treatment. The complete occlusion rate of APS in Gelfoam group was 18.2%(6/33) totally.

The recanalization rate of APS in ethanol group was lower than that in Gelfoam group (χ^2=24.91, $P<0.05$), and the complete occlusion rate of APS in ethanol group was higher than that in Gelfoam group (χ^2=32.06, $P<0.05$).

Survival

The survival rate in the ethanol group were 78% at 6 mo, 49% at 12 mo, and 25% at 24 mo. The median survival was 11 mo. By comparison, the survival rates in the Gelfoam group were 58% at 6 mo, 29% at 12 mo, 15% at 24 mo, and the median survival was 7 mo. The survival rates in the ethanol group were significantly higher than those in the Gelfoam group ($P<0.05$) (Figure 2).

In the ethanol group, the survival rates of patients with single HCC nodule were 92% at 6 mo, 70% at 12 mo, and 55% at 24 mo. The survival rates of patients with two or three HCC nodules were 73% at 6 mo, 55% at 12 mo and 22% at 24 mo. The survival rates of patients with multiple HCC nodules or diffuse HCC were 68% at 6 mo, 33% at 12 mo and 15% at 24 mo. The survival rates of patients with monofocal HCC were significantly higher than those of patients with multifocal HCC ($P<0.05$) (Figure 3). The survival rates of patients of Child class A were 91% at 6 mo, 60% at 12 mo, and 38% at 24 mo. The survival rates of patients of Child class B were 62% at 6 mo, 35% at 12 mo and 13% at 24 mo. The survival rates of patients of Child class A were higher than those of patients of Child class B ($P<0.05$) (Figure 4).

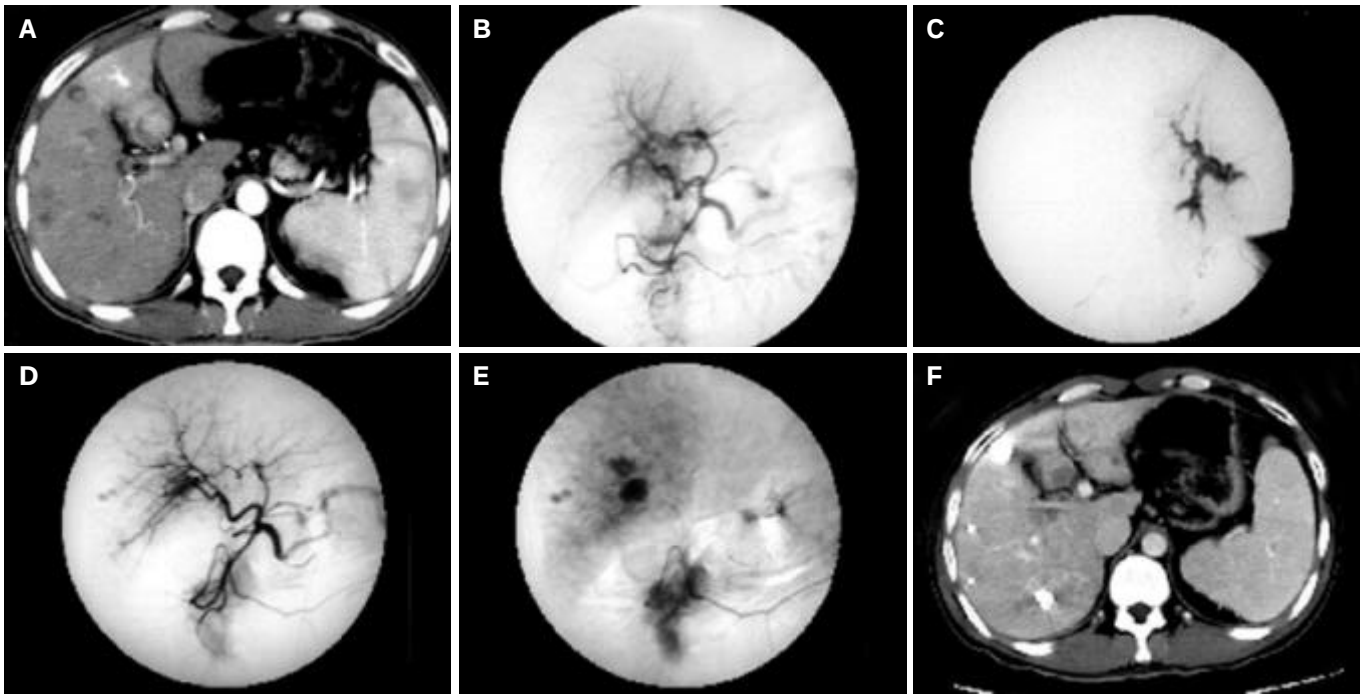

Figure 1 Multiple HCC nodules in a 34-year-old patient. A: CT image obtained during the arterial phase showed the predominant enhancement of the medial segment of left lobe and the enhancement of left portal branches, which represent APS. B: Hepatic arteriogram demonstrated the arterioportal shunt. C: The microcatheter was inserted into the feeding artery of APS. DSA showed the strong or fast blood flow of APS. D-E: Hepatic arteriogram showed that the arterioportal shunt was no longer visible after embolization with a microcoil and ethanol. F: Follow-up CT scan showed lipiodol accumulation in multiple HCC nodules, and liver necrosis was not seen in the distribution of the hepatic artery which had been treated with ethanol.

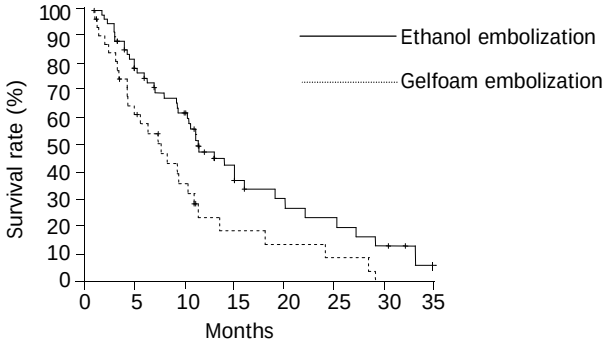

Figure 2 Cumulative survival curves for patients with HCC and APS in two therapeutic groups are shown. The survival rates for patients in the ethanol group were significantly higher than those in the Gelfoam group (P<0.05).

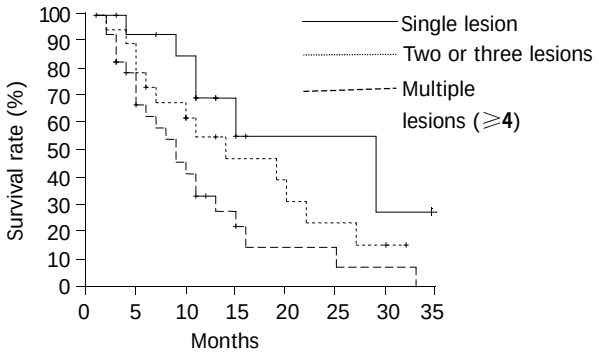

Figure 3 Cumulative survival curves for patients with HCC and APS in relation to number of tumors are shown in ethanol group. The survival rates of patients with monofocal HCC and APS were significantly higher than those of patients with multifocal HCC and APS (single lesion *vs* two or three lesions, P<0.05; two or three lesions *vs* four or more lesions, P<0.05).

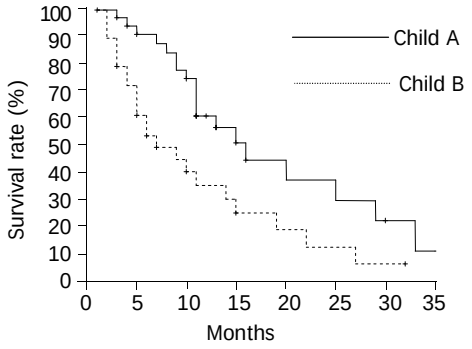

Figure 4 Cumulative survival curves for patients with HCC and APS according to the Child class were shown in ethanol group. The survival rates of patients of Child class A were higher than those of Child class B (P<0.05).

In the Gelfoam group, the survival rates of patients with single HCC nodule were 62% at 6 mo, 38% at 12 mo, and 19% at 24 mo. The survival rates of patients with two or three HCC nodules were 61% at 6 mo, 26% at 12 mo and 12% at 24 mo. The survival rates of patients with multiple HCC nodules or diffuse HCC were 60% at 6 mo, 28% at 12 mo and 0 at 24 mo. The survival rates of patients of Child class A were 60% at 6 mo, 25% at 12 mo, and 18% at 24 mo. The survival rates of patients of Child class B were 68% at 6 mo, 30% at 12 mo and 15% at 24 mo. There were no significant differences in survival rates with regard to the number of tumor, and Child class (P>0.05).

Side effects and complications

In the ethanol group, a short-period intense abdominal pain occurred in 53(82.8%) patients during the process of ethanol injection, and mild abdominal pain in 9(14.1%) patients, and indolence in 2(3.1%) patients. Postembolization syndromes (such as nausea, vomiting, fever, and abdominal pain) occurred

in 50(78.1%) patients in ethanol group, and 30(90.9%) patients in Gelfoam group. There was no significant difference between the 2 groups (χ^2=1.66, P>0.05). No patient died of procedure-related hepatic failure. In ethanol group, all feeding artery remained patent in the follow-up DSA arteriograms, and liver necrosis in the distribution of the hepatic artery which had been treated with ethanol was not seen in all patients according to the follow-up CT scans.

DISCUSSION

Hepatocellular carcinoma is frequently associated with arterioportal shunts. In our series, severe APSs were verified in 27% of patients with HCC by DSA. Severe APS leads to or aggravates portal hypertension which leads to life-threatening conditions such as esophageal varices, refractory ascites, refractory diarrhea and hepatic encephalopathy[4-7,16,17]. Additionally, severe APSs have an influence on the performance of TAI or TACE for the treatment of HCC[18]. The persistence of APS may possibly result in the poor prognosis of HCC. For the reasons as above, severe APS needs to be treated effectively.

Many embolic materials have been used to treat APS in patients with HCC[8,9,19-23]. Of those Gelfoam and steel coil were the most commonly used. Clark[9] and Tarazov[8] reported that Gelfoam and steel coil emboli for the treatment of APS could not prolong the survival of patients with HCC, although they had a good short-term effect on the control of gastric bleeding and ascites. Those effects may be attributable to certain actions of those embolic materials. Firstly, Gelfoam embolization was likely to result in inadvertent embolization, and cause the occlusion of feeding artery of tumor, which would influence the procedure of TAI or TACE for the treatment of tumor. Secondly, the recanalization of APS occurred easily as a result of the development of collateral vessels and the absorption of Gelfoam two to four weeks after embolization. In our study, the recanalization rate of APS was 85.7% 1 month after embolization with Gelfoam. Similarly, the embolization with steel coil also produced the recanalization of APS as a result of the development of collateral anastomoses[8].

Ethanol is a liquid embolic agent that causes immediate vascular sclerosis and occlusion by a combination of direct toxic effect on the vascular wall and clumping of damaged erythrocytes and denatured proteins[24-26]. It has been used widely in the treatment of renal cell carcinoma, esophageal varices, and arteriovenous malformations[24-35]. Similar to the treatment of arteriovenous malformation, injecting ethanol into APS results in clot formation, denudes the endothelium and causes embolization by penetrating into the capillaries. As an embolic material, ethanol is superior to Gelfoam in the treatment of APS. First, ethanol can pass to and occlude the capillaries and veins of shunt, and does not lead to the occlusion of feeding artery of tumor. Thus it produces a more complete occlusion of APS than Gelfoam. Second, ethanol is a kind of long-acting embolic material, and it rarely develops the collateral anastomoses after embolization with ethanol. It has a low recanalization rate of APS. Third, ethanol also has a direct tumoricidal effect. Our results showed the recanalization rate of APS 1 month after embolization with ethanol was 17.8%, and complete occlusion rate was 82.8%, which were better than those of Gelfoam group (P<0.05).

Furuse *et al*[10] reported that the survival rate of patients with HCC and APS after steel coil embolization were 45% at 6 mo, 12% at 12 mo, and 6% at 2 yr, and it could not prolong the survival of patient with HCC after the treatment of APS. However, Liu *et al*[36] reported that the survivals of HCC patients without APS were higher than those of patients with APS. It indicated that the persistence of APS was an important prognostic factor. In our study, the complete occlusion rate of shunt in ethanol group was higher than that in Gelfoam group (P<0.05). The survival rate of patients in the ethanol group was 78% at 6 mo, 49% at 12 mo, 25% at 24 mo, which were higher than those of Gelfoam group (P<0.05). Our results suggest that the embolization of APS with ethanol provides a survival advantage over that with gelfoam in patient with HCC. In addition, there was a significant prolongation of survival in patients with monofocal HCC and Child class A in ethanol group (P<0.05). However, there were no significant differences in survival rates in Gelfoam group with regard to the differences in the number of tumor and Child class (P>0.05). It was suggested that the survival rate was also related to the stage and invasive extent of tumor, and general state of patients. On the other hand, the persistence of severe APS was the important factor which influenced the survival of patient with HCC and APS.

The most common complication of embolization of APS with ethanol was abdominal pain caused by destruction of the vascular endothelium when ethanol was injected[24,25]. The incidence was 82.8% in our study. It could be alleviated immediately when we stopped injecting ethanol. There was no severe complication related to ethanol embolization. In our study, liver necrosis was not seen in the distribution of the hepatic artery which had been treated with ethanol in the follow-up CT scans. The postembolization syndromes were related to the specific treatment of tumor, and there was no significant difference between the two groups.

In conclusion, ethanol embolization for patients with HCC and severe APS is efficacious and safe, and may contribute to prolongation of the life span versus Gelfoam embolization.

ACKNOWLEDGMENTS

We thank David A. Kumpe, MD, from the Health Sciences Center, University of Colorado Derver, USA, for his assistance in revising the manuscript.

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Edited by Zhu LH **Proofread by** Xu FM