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RAPID COMMUNICATION

Combined treatment of hepatocellular carcinoma with partial splenic embolization and transcatheter hepatic arterial chemoembolization

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Abstract

AIM: To prospectively evaluate the efficacy and safety of partial splenic embolization (PSE) combined with transcatheter hepatic arterial chemoembolization (TACE) in treatment of hepatocellular carcinoma (HCC).

METHODS: Fifty patients suffering from primary HCC associated with hypersplenism caused by cirrhosis were randomly assigned to 2 groups: group A receiving PSE combined with TACE (n = 26) and group B receiving TACE alone (n = 24). Follow-up examinations included calculation of peripheral blood cells (leukcytes, platelets and red blood cells) and treatment-associated complications.

RESULTS: Prior to treatment, there was no significant difference in sex, age, Child-Pugh grade, tumor diameter, mass pathology type and peripheral blood cell counts between the 2 groups. After treatment, leukocyte and platelet counts were significantly higher in group A during the 3-mo follow-up period ($P < 0.05$), but lower in group B ($P < 0.05$). Severe complications occurred in 3 patients (11.5%) of group A and in 19 patients (79.2%) of group B ($P < 0.05$), and there was no significant difference in symptoms of post-embolization syndrome, including abdominal pain, fever, mild nausea and vomiting between the 2 groups ($P > 0.05$).

CONCLUSION: PSE combined with TACE is more effective and safe than TACE alone for patients with HCC associated with hypersplenism caused by cirrhosis.

Key words: Hepatocellular carcinoma; Hypersplenism; Cirrhosis; Partial splenic embolization; Transcatheter hepatic arterial chemoembolization

INTRODUCTION

Transcatheter hepatic arterial chemoembolization (TACE) has become the first choice of treatment for unresectable hepatocellular carcinoma (HCC)[1-4]. Since 70%-90% of HCC patients are associated with liver cirrhosis, portal hypertension and hypersplenism, treatment of HCC is usually affected by low peripheral blood cell counts (leukcytes, platelets and red blood cells) and high incidence of hemorrhagic complications due to treatment and/or portal hypertension[5-8]. Moreover, chemotherapeutics during TACE is another cause for low peripheral blood cell counts because of myelosuppression. Partial splenic embolization (PSE), which is thought to be an effective alternative to splenomegaly[9,10] because of its milder injury and fewer complications, has been widely used in treatment of leukocytopenia and thrombocytopenia caused by splenomegaly since the report of Maddison in 1973[11].

MATERIALS AND METHODS

Patients

From December 2002 to May 2006, 50 consecutive patients with HCC associated with hypersplenism caused by liver cirrhosis and portal hypertension were enrolled in this study. The diagnosis of HCC was established on the basis of clinical laboratory data, computed tomography and biopsy. The diagnosis of hypersplenism and splenomegaly was made in the light of clinical laboratory data and computed tomography. The enrolling criteria for this study were patients with splenomegaly and thrombocytopenia (platelet count $\leqslant 60 \times 10^9$/L) and/or leukocytopenia (leukocyte count $\leqslant 3.0 \times 10^9$/L). Adequate supporting therapies were performed for patients having severe peritonealgia before treatment with PSE and TACE or TACE alone in order to decrease the amount of ascites. Patients meeting the above criteria were randomly assigned to either group A or group B based on the computer-generated randomization sequences. Of the 50 patients,

Table 1 Demographic, clinical, histological and laboratory characteristics of patients *n* (%)

Characteristics	Group A, *n*	Group B	*P*-value
Patients	26	24	
Sex			
Male	19 (73)	18 (75)	0.877[1]
Female	7 (27)	6 (25)	
Age (yr)	44.1 ± 12.1	45.0 ± 9.0	0 .760[2]
Child-Pugh grade			
A	2 (8)	2 (8)	
B	20 (77)	19 (79)	0.806[1]
C	4 (15)	3 (13)	
Pathology type			
Mass type	14 (54)	14 (58)	0.834[1]
Node type	10 (38)	8 (33)	
Diffusion type	2 (8)	2 (8)	
Tumor diameter (cm)			
Peripheral blood cell counts	4.64 ± 2.34	4.44 ± 2.58	0.780[2]
WBC ($\times 10^9$)	2.45 ± 0.41	2.40 ± 0.51	0.734[2]
PLT ($\times 10^9$)	45.95 ± 9.49	45.02 ± 8.96	0.723[2]
RBC ($\times 10^{12}$)	3.02 ± 0.49	3.07 ± 0.51	0.750[2]

[1]Data are determined with the χ^2 test; [2]Data are determined with the *t*-test.

26 received PSE in combination with TACE (group A), 24 received TACE alone (group B).The characteristics of these patients are summarized in Table 1.

Methods

The patients in group A were treated with PSE and TACE, first with PSE, and then with TACE, while the patients in group B received TACE alone.

PSE was performed as follows. In brief, a 5.0 French catheter (Terumo, Tokyo, Japan) was inserted into the femoral artery by the Seldinger method, celiac angiography and selective splenic arterial angiography were routinely performed to observe the distribution of splenic arteries and collateral circulation routes (Figure 1A), the tip of the catheter was placed as distal as possible at the hilus of the spleen, and embolization was performed using gelfoam particles (1-2 mm) suspended in an antibiotic solution (16 mg gentamicin sulfate) and contrast medium. The extent of embolization was set at 50%-70%. To achieve this, embolization was performed progressively by means of repeated injections of gelfoam particles under angiography control. Immediate angiography was done after each injection and the extent of embolization was expressed as the percentage of the ablated splenic parenchyma area shown by post-embolization angiography against the total splenic parenchyma area given by pre-embolization angiography. When a 50%-70% ablation of the splenic parenchyma was obtained (Figure 1B), the embolization was terminated. The extent of embolization was simultaneously estimated on angiography. In case the two estimates failed to agree, the mean value was taken. Finally, the precise extent of embolization was determined by CT scan 2 wk later.

Under strict conditions, TACE was performed as follows. In brief, a 5.0 French catheter (Terumo, Tokyo, Japan) was inserted into the femoral artery with the Seldinger method, celiac angiography and selective hepatic arterial angiography were routinely performed to observe the tumor blood-supply, distribution of hepatic arteries and collateral circulation routes (Figure 1C), the tip of the catheter was placed at the feeding artery of the tumor, and embolization was performed using an emulsion mixture of lipoidal ultra-fluid (Guerbet, France), perarubicin (50 mg/m^2) and DDP (80 mg/m^2). The maximum dose for embolization was based on the size of the tumor, blood supply and hepatic function of the patient. When the tumor was filled well with emulsifier, the embolization was terminated (Figure 1D).

Follow-up protocol

All patients underwent abdominal CT scanning (Light Speed QX/I CT scanner, GE Medical Systems, Milwaukee, Wis) 1 wk before operation (Figure 1E). Patients in group A also underwent abdominal CT scanning (Light Speed QX/L CT scanner,GE Medical Systems,Milwaukee,Wis) 2 wk after PSE/TACE treatment (Figure 1F). The extent of embolization (%) was determined by dividing the infarction volume, which is the whole splenic volume minus the residual splenic volume, by the whole splenic volume based on the CT examination 2 wk after PSE/TACE treatment.

After treatment with PSE in combination with TACE or with TACE alone, all patients remained in the hospital with their severe complications observed and were then followed up at the Outpatient Clinic. Peripheral blood cell parameters including white blood cells (WBC), platelets (PLT) and red blood cells (RBC) in group A after PSE/TACE treatment and in group B after TACE treatment were respectively monitored during the 1-wk, 2-wk, 1-mo, 2-mo and 3-mo follow-up after PSE/TACE treatment.

Statistical analysis

All data were analyzed using the SAS software (Vertion 8.1, SAS Institute, Cary, NC). Significance was established at $P < 0.05$. To determine statistically significant difference between the two groups, the *t*-test or the χ^2 test was used. The paired *t*-test was used to determine the difference in group A before and after PSE/TACE treatment and in group B before and after TACE treatment, and between groups A and B after treatment.

RESULTS

Chronological changes in peripheral blood cell counts

No significant difference was found in sex, age, Child-Pugh grade, tumor diameter, mass pathology type and peripheral blood cell counts between the 2 groups (Table 1). The peripheral blood cell counts before PSE/TACE or TACE treatment and from the third day to the forth week after PSE treatment are listed in Tables 2, 3 and 4. There were no significant differences in WBC, PLT and RBC counts between the 2 groups before PSE/TACE or TACE treatment ($P > 0.05$). There were significant differences in WBC and PLT counts before and after PSE/TACE treatment ($P < 0.001$, Tables 2 and 3). WBC and PLT counts were significantly higher from the first week to the third month after PSE/TACE treatment. There were significant differences in WBC and PLT counts before and

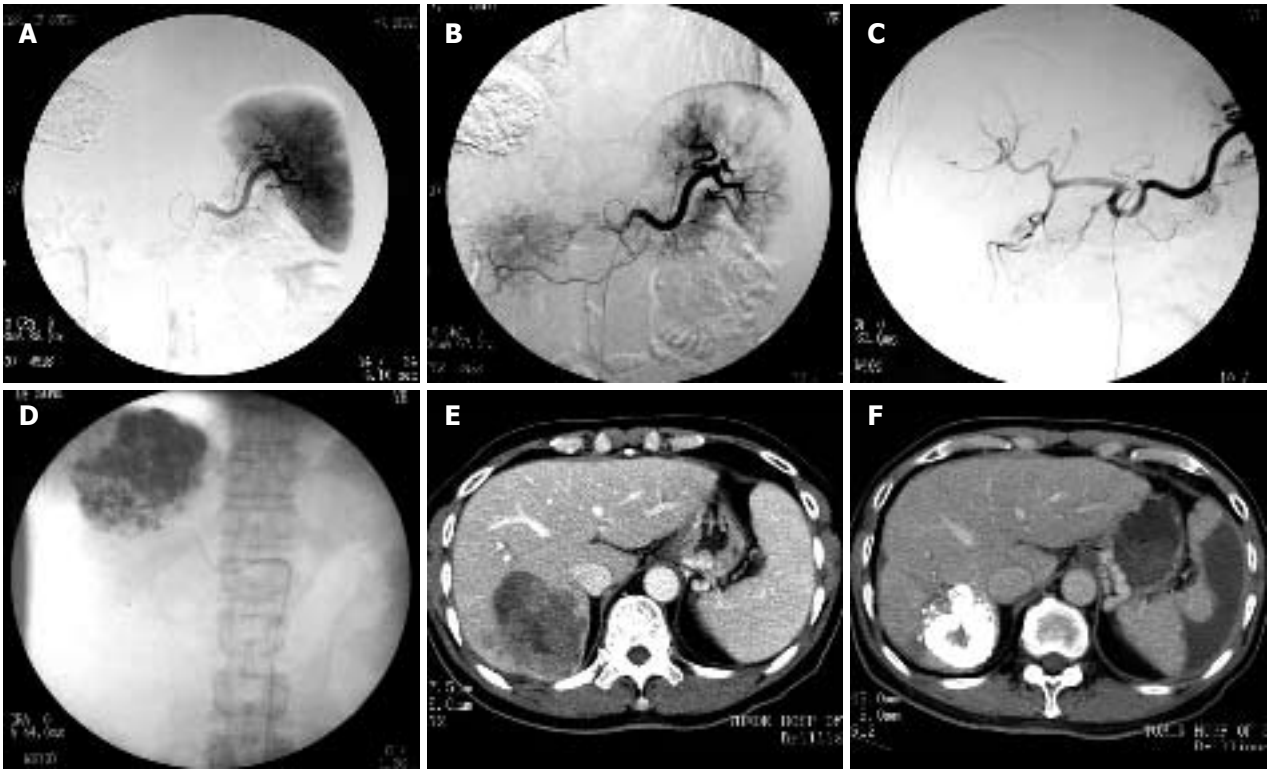

Figure 1 PSE treatment for a 68-year-old male case of HCC with splenomegaly and thrombocytopenia. **A**: Splenic arteriography before PSE showing the whole splenic parnchymal image; **B**: Splenic arteriography after PSE showing the residual splenic parnchymal image, part of the peripheral splenic parenchyma was ablated, and the extent of embolization was roughly estimated of approximately 60%; **C**: Celiac arteriography before TACE showing the tumor blood-supply image; **D**: TACE is terminated when the tumor is filled with emulsifier; **E**: Transverse CT image revealing splenomegaly at 1 wk before PSE/TACE; **F**: Transverse CT image revealing the infarction of peripheral splenic parenchyma at 2 wk after PSE. The extent of embolization was 62% calculated by CT volume analysis software.

Table 2 Follow-up results of WBC counts ($\times 10^9$/L)

Time	Group A		Group B		*P*-value[2]
	mean ± SD	*P*-value[1]	mean ± SD	*P*-value[1]	
Pre-treatment	2.45 ± 0.41		2.40 ± 0.51		0.734
Post-treatment					
1 wk	7.26 ± 0.96	< 0.001	1.77 ± 0.38	< 0.001	< 0.001
2 wk	6.42 ± 1.02	< 0.001	1.68 ± 0.39	< 0.001	< 0.001
1 mo	6.31 ± 0.83	< 0.001	1.72 ± 0.65	< 0.001	< 0.001
2 mo	6.03 ± 0.93	< 0.001	1.91 ± 0.73	0.0032	< 0.001
3 mo	5.36 ± 0.64	< 0.001	2.02 ± 0.48	0.013	< 0.001

[1]Comparison of WBC counts before and after treatment at different time points within each group; [2]Comparison of WBC counts between the two groups at different time points determined with *t*-test.

Table 3 Follow-up results of PLT counts ($\times 10^9$/L)

Time	Group A		Group B		*P*-value[2]
	mean ± SD	*P*-value[1]	mean ± SD	*P*-value[1]	
Pre-treatment	45.95 ± 9.49		45.02 ± 8.96		0.723
Post-treatment					
1 wk	169.21 ± 26.55	< 0.001	28.56 ± 5.11	< 0.001	< 0.001
2 wk	136.50 ± 13.12	< 0.001	26.62 ± 7.31	< 0.001	< 0.001
1 mo	133.46 ± 16.21	< 0.001	27.46 ± 6.29	< 0.001	< 0.001
2 mo	125.73 ± 18.35	< 0.001	31.06 ± 6.70	< 0.001	< 0.001
3 mo	119.86 ± 12.43	< 0.001	33.15 ± 6.91	< 0.001	< 0.001

[1]Comparison of PLT counts before and after treatment at different time points within each group; [2]Comparison of PLT counts between the two groups at different time points determined with *t*-test.

after TACE treatment in group B ($P < 0.05$, Tables 2 and 3). WBC and PLT counts were significantly lower in group B from the first week to the third month after TACE treatment. There were significant differences in WBC and PLT counts between groups A and B ($P < 0.001$, Tables 2 and 3). WBC and PLT counts were significantly higher in group A after PSE/TACE treatment than in group B from the first week to the third month after TACE treatment. However, there were no significant differences in RBC counts between the 2 groups ($P > 0.05$, Table 4).

Complications

Symptoms of post-embolization syndrome, including abdominal pain, fever and mild nausea and vomiting, occurred in our patients. Abdominal pain was found in 76.9% (20/26) patients of group A and was alleviated by durogesic or oxycodone, in 75.0% (18/24) patients of group B and was alleviated by Tramadol with no significant differences between the two groups. The incidence of fever was 84.6% (22/26) in group A and was lowered by dexamethasone, 83.3% (20/24) in group B and was lowered by salicylic acid drugs with no significant differences between the two groups. The incidence of mild nausea and vomiting was 19.2% (20/26) in group A, 25.0% (6/24) in group B with no significant differences between the two groups. Severe complications occurred in 3 patients (11.5%) of group A, in 19 patients (79.2%) of group B (Table 5). A large amount of pleural effusion

Table 4 Follow-up results of RBC counts ($\times 10^{12}$/L)

Time	Group A		Group B		*P*-value[2]
	mean ± SD	*P*-value[1]	mean ± SD	*P*-value[1]	
Pre-treatment	3.02 ± 0.49		3.07 ± 0.51		0.75
Post-treatment					
1 wk	2.84 ± 0.72	0.297	2.93 ± 0.56	0.375	0.639
2 wk	2.88 ± 0.54	0.325	2.97 ± 0.68	0.583	0.606
1 mo	2.81 ± 0.36	0.073	2.93 ± 0.71	0.442	0.430
2 mo	2.92 ± 0.42	0.418	2.85 ± 0.62	0.185	0.623
3 mo	3.04 ± 0.50	0.924	2.97 ± 0.47	0.439	0.644

[1]Comparison of RBC counts before and after treatment at different time points within each group; [2]Comparison of RBC counts between the two groups at different time points determined with *t*-test.

Table 5 Complications observed in 50 patients 2 wk after treatment *n* (%)

Complications	Group A	Group B	*P*-value
Abdominal pain	20 (76.9)	18 (75.0)	0.874[1]
Fever	22 (84.6)	20 (83.3)	0.903[1]
Mild nausea and vomiting	5 (19.2)	6 (25.0)	0.623[1]
Large amount of pleural effusion or ascites	1 (3.9)	6 (29.2)	0.016[1]
Bacterial peritonitis	1 (3.9)	6 (25.0)	0.033[1]
Variceal bleeding	1 (3.9)	7 (29.2)	0.016[1]

[1]Data are determined with the χ^2 test.

and ascites was found in 1 patient of group A and in 6 patients of group B, leading to dyspnea or abdominal pain which was resolved by thoracentesis and paracentesis. Bacterial peritonitis occurred in 1 patient of group A and in 6 patients of group B 1 mo after PSE treatment. Variceal bleeding was observed in 1 patient of group A and in 7 patients of group B and was controlled by conservative therapy. There were significant differences in severe complications between the 2 groups ($P < 0.05$, Table 5). The occurrence of severe complications such as pleural effusion or ascites, bacterial peritonitis and variceal bleeding was significantly higher in group B than in group A after treatment.

DISCUSSION

HCC is often associated with hypersplenism due to liver cirrhosis. In such cases, it is very difficult to perform TACE because of the high incidence of hemorrhagic complications and/or portal hypertension, as well as poor tolerance of cirrhotic patients to chemotherapeutic drugs[12]. PSE is a useful support therapy for portal hypertension or hypersplenism and has taken the place of surgical splenectomy[9,10,13,14]. PSE appears to be effective in reducing episodes of variceal bleeding, improving hematologic parameters, enhancing hepatic protein synthesis, and reducing the severity of hepatic encephalopathy[15-18]. Roversi *et al*[12] reported that complications such as pleural effusion or ascites, bacterial peritonitis and variceal bleeding occurred in six patients with nodular HCC and cirrhosis (Child B) after treated with TACE in combination with PSE. In our study, thrombocytes, leucocytes and erythrocytes increased markedly, severe complications occurred in 3 patients (11.5%) of group A and in14 patients (79.2%) of group B. N'Kontchou *et al*[19] showed that severe complications occurred in six patients (16%) in their study, namely transient ascites in 2, splenic and/or portal vein thrombosis in 2, and splenic abscess in 2. Sakai *et al*[20] observed two cases suffering from severe complications after PSE treatment in 17 patients with cirrhosis. Other severe complications of PSE treatment such as pleural effusion, rupture of spleen, portal vein thrombosis have also been reported[13,21,22].

In this study, embolization ranged from 50% to 70%. Lee *et al*[23] reported that there are significant differences in platelet values between low and high embolization areas in patients with cirrhosis. The complication rate for < 30% and > or = 30% embolization areas is 50% and 100%, respectively. In our study, severe complications had a close relationship with the extent of embolization of the spleen. Among the 4 patients with an embolization of over 70%, 3(75%) developed severe complications. On the contrary, among the 22 patients with embolization of 70% or lower, only 1 (5%) developed severe complications, suggesting that PSE should be strictly limited to less than 70% of the splenic volume in order to reduce severe complications.

Gelfoam particles are the most commonly used embolic material in PSE [9,10,13,14,24-26], and extensive research has confirmed the short- or long-term efficacy of PSE using gelfoam particles as embolic material[9,13,14,25]. N' Kontchou *et al*[19] also performed PSE using PVA particles as embolic material (200-1000 μm in diameter) in patients with cirrhosis, but the efficacy and safety were uncertain, especially the long-term efficacy in peripheral blood cell count and safety. In this study, we used gelfoam particles as embolic material in PSE and achieved good results, indicating that gelfoam particles are safe materials in PSE.

In conclusion, combined one-step TACE/PSE treatment can improve the tolerance of HCC patients with advanced/decompensated cirrhosis and hypersplenism to chemotherapeutic drugs and reduce the risk of complications of invasive radiologic procedures and/or portal hypertension. PSE may resolve cytopenia and clinical complications related to hypersplenism or splenomegaly. However, due to severe complications, particularly splenic abscess, the indications for PSE should be limited and the extent of necrosis should be controlled during the PSE procedure.

COMMENTS

Background

In many cases of hepatocellular carcinoma (HCC) associated with liver cirrhosis and hypersplenism, it is very difficult to perform TACE because of the high incidence of hemorrhagic complications and poor tolerance of patients to chemotherapeutic drugs. The combined one-step TACE/PSE treatment can improve the tolerance of patients to chemotherapeutic drugs and reduce hemorrhagic complications of invasive radiologic procedures and/or portal hypertension.

Research frontiers

In this study, hematologic parameters and severe complications such as pleural effusion or ascites, bacterial peritonitis and variceal bleeding were observed. PSE may resolve cytopenia and clinical complications related to hypersplenism

or splenomegaly. Embolization and embolic material in PSE have not been standardized, but in our study, 50% to 70% of embolization was achieved with gelfoam particles as embolic material.

Innovations and breakthroughs

TACE has become the best choice of treatment for unresectable HCC. PSE may resolve cytopenia and clinical complications related to hypersplenism or splenomegaly. However, there have been few reports on the feasibility and effects of the combined one-step TACE/PSE treatment in cases of HCC associated with liver cirrhosis and hypersplenism.

Applications

Based on the results of our study, PSE in combination with TACE is more effective and safer for patients with HCC associated with hypersplenism caused by cirrhosis than TACE alone.

Terminology

TACE, an abbreviation of transcatheter hepatic arterial chemoembolization, is now widely used in treatment of HCC. PSE means partial splenic embolization.

Peer review

This paper provides some information about combining splenic embolization with TACE for gastroenterologists, hepatologists, and interventional radiologists.

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