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

Jin-Hua Huang, Fei Gao, Yang-Kui Gu, Wen-Quan Li, Lian-Wei Lu

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 (leukocytes, 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.

© 2007 WJG. All rights reserved.

Key words: Hepatocellular carcinoma; Hypersplenism; Cirrhosis; Partial splenic embolization; Transcatheter hepatic arterial chemoembolization
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 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/m²) and DDP (80 mg/m²). 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, Wisconsin, Wis) 1 wk before operation (Figure 1E). Patients in group A also underwent abdominal CT scanning (Light Speed QX/I 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 (Version 8.1, SAS Institute, Cary, NC). Significance was established at $P \leq 0.05$. To determine statistically significant difference between the two groups, the $t$-test or the $\chi^2$ 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**

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 fourth 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 after PSE/TACE treatment.

### Table 1: Demographic, clinical, histological and laboratory characteristics of patients $n$ (%)

| Characteristics                | Group A, $n$ | Group B, $n$ | $P$-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)     |          |
| C                             | 4 (15)      | 3 (13)      |          |
| Pathology type                |             |             |          |
| Mass type                     | 14 (54)     | 14 (58)     | 0.834$^3$|
| Node type                     | 10 (38)     | 8 (33)      |          |
| Diffusion type                | 2 (8)       | 2 (8)       |          |
| Tumor diameter (cm)           |             |             |          |
| Peripheral blood cell counts  |             |             |          |
| WBC ($\times 10^9$)           | 4.64 ± 2.34 | 4.44 ± 2.58 | 0.780$^3$|
| PLT ($\times 10^9$)           | 2.45 ± 0.41 | 2.40 ± 0.51 | 0.734$^4$|
| RBC ($\times 10^6$)           | 45.95 ± 9.49| 45.02 ± 8.96| 0.723$^2$|

$^1$Data are determined with the $\chi^2$ test; $^2$Data are determined with the $t$-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

![Figure 1](https://www.wjgnet.com/Huang.JH/Treatment.of.HCC.with.PSE.and.TACE.6595)
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. PSE is a useful support therapy for portal hypertension and has taken the place of surgical splenectomy. 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. Roversi et al 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 in 14 patients (79.2%) of group B. N’Kontchou et al 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 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. In this study, embolization ranged from 50% to 70%. Lee et al 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, and extensive research has confirmed the short- or long-term efficacy of PSE using gelfoam particles as embolic material. N’Kontchou et al 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.

---

### Table 4 Follow-ups of RBC counts ( × 10^12/L)

| Time      | Group A | Group B | P-value* |
|-----------|---------|---------|----------|
| 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 |

*Comparison of RBC counts before and after treatment at different time points within each group; **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 |
| Fever                   | 22 (84.6) | 20 (83.3) | 0.903 |
| Mild nausea and vomiting | 5 (19.2) | 6 (25.0) | 0.623 |
| Large amount of pleural effusion or ascites | 1 (3.9) | 6 (29.2) | 0.016 |
| Bacterial peritonitis   | 1 (3.9) | 6 (25.0) | 0.033 |
| Variceal bleeding       | 1 (3.9) | 7 (29.2) | 0.016 |

*Data are determined with the χ² test.
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.

**REFERENCES**

1. Miraglia R, Pietrosi G, Maruzzelli L, Petridis I, Caruso S, Marrone G, Mamone G, Vizzini G, Luca A, Gridelli B. Efficacy of transcatheter embolization/chemoembolization (TAE/TACE) for the treatment of single hepatocellular carcinoma. *World J Gastroenterol* 2007; 13: 2952-2955

2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; 362: 1907-1917

3. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004; 127: S179-S188

4. Lubieniski A. Hepatocellular carcinoma: interventional bridging to liver transplantation. *Transplantation* 2005; 80: SI13-SI19

5. Han MJ, Zhao HG, Ren K, Zhao DC, Xu K, Zhang XT. Partial splenic embolization for hypersplenism concomitant with or after arterial embolization of hepatocellular carcinoma in 30 patients. *Cardiovasc Intervent Radiol* 1997; 20: 125-127

6. Ohmoto K, Yamamoto S. Prevention of variceal recurrence, bleeding, and death in cirrhosis patients with hypersplenism, especially those with severe thrombocytopenia. *Hepatogastroenterology* 2003; 50: 1766-1769

7. Miyayama S, Matsu O, Kadoya M, Hirose J, Kameyama T, Chohotou S, Konishi H, Takashima T, Kobayashi K, Hattori S. Long-term effects of partial splenic embolization (PSE) for hypersplenism. *Rinsho Hoshasen* 1989; 34: 893-898

8. Hirai K, Kawazoe Y, Yamashita K, Kumagai M, Tanaka M, Sakai T, Inoue R, Eguchi S, Majima Y, Abe M. Transcatheter partial splenic arterial embolization in patients with hypersplenism: a clinical evaluation as supporting therapy for hepatocellular carcinoma and liver cirrhosis. *Hepatogastroenterology* 1986; 33: 105-108

9. Tajiri T, Onda M, Yoshida H, Mamada Y, Taniai N, Kumazaki T. Long-term hematological and biochemical effects of partial splenic embolization in hepatic cirrhosis. *Hepatogastroenterology* 2002; 49: 1445-1448

10. Kimura F, Ito H, Shimizu H, Togawa A, Otsuka M, Yoshidome H, Shimamura F, Kato A, Nukui Y, Ambiru S, Miyazaki M. Partial splenic embolization for the treatment of hereditary spheroerythrocytosis. *AJR Am J Roentgenol* 2003; 181: 1021-1024

11. Maddison F. Embolic therapy of hypersplenism. *Invest Radiol* 1973; 8: 280-281

12. Roversi R, Ricci S, Gambari PL, Castaldini L, Rossi G, Milandri G, Formica G, Dalmonte PR. [Splenic embolization and hepatic chemoembolization: combined transcatheter treatment of hepatocellular carcinoma in cirrhosis with hypersplenism]. *Radiol Med* 1993; 85: 444-449

13. Sakata K, Hirai K, Tanikawa K. A long-term investigation of transcatheter splenic arterial embolization for hypersplenism. *Hepatogastroenterology* 1996; 43: 309-318

14. Sangro B, Bilbao I, Herrero I, Corella C, Longo J, Belouqi O, Ruiz J, Zozaya JM, Quiroga J, Prieto J. Partial splenic embolization for the treatment of hypersplenism in cirrhosis. *Hepatology* 1993; 18: 309-314

15. Koconis KG, Singh H, Soares G. Partial splenic embolization in the treatment of patients with portal hypertension: a review of the English language literature. *J Vasc Interv Radiol* 2007; 18: 463-481

16. Shimizu T, Onda M, Tajiri T, Yoshida H, Mamada Y, Taniai N, Aramaki T, Kumazaki T. Bleeding portal-hypertensive gastropathy managed successfully by partial splenic embo- lization. *Hepatogastroenterology* 2002; 49: 947-949

17. Romano M, Giojelli A, Capuano G, Pomponi D, Salvatore M. Partial splenic embolization in patients with idiopathic portal hypertension. *Eur J Radiol* 2004; 49: 268-273

18. Pålsson B, Hallen M, Forsberg AM, Almwall A. Partial splenic embolization: long-term outcome. *Langenbecks Arch Surg* 2003; 387: 421-426

19. N’Kontchou G, Seror O, Bourvich V, Mohand D, Ajavon Y, Castera L, Grando-Lemaire V, Ganne-Carrie N, Sellier N, Trinchet JC, Beaugrand M. Partial splenic embolization in patients with cirrhosis: efficacy, tolerance and long-term outcome in 32 patients. *Eur J Gastroenterol Hepatol* 2005; 17: 179-184

20. Sakai T, Shiraiki K, Inoue H, Sugimoto K, Ohmori S, Murata K, Takase K, Nakano T. Complications of partial splenic embolization in cirrhotic patients. *Dig Dis Sci* 2002; 47: 388-391

21. Wholey MH, Chamorro HA, Rao G, Chapman W. Splenic infarction and spontaneous rupture of the spleen after therapeutic embolization. *Cardiovasc Radiol* 1978; 1: 249-253

22. Owman T, Lunderquist A, Almwall A, Borjesson B. Embolization of the spleen for treatment of splenomegaly and hypersplenism in patients with portal hypertension. *Invest Radiol* 1979; 14: 457-464

23. Lee CM, Leung TK, Wang HJ, Lee WH, Shen LK, Liu JD, Chang CC, Chen YY. Evaluation of the effect of partial splenic embolization on platelet values for liver cirrhosis patients with thrombocytopenia. *World J Gastroenterol* 2007; 13: 619-622

24. Noguchi H, Hirai K, Aoki Y, Sakata K, Tanikawa K. Changes in platelet kinetics after a partial splenic arterial embolization in cirrhotic patients with hypersplenism. *Hepatology* 1995; 22: 1682-1688

25. Murata K, Shiraiki K, Takase K, Nakano T, Tameda Y. Long term follow-up for patients with liver cirrhosis after partial splenic embolization. *Hepatogastroenterology* 1996; 43: 1212-1217

26. Yoshida H, Mamada Y, Taniai N, Yamamoto K, Kaneko M, Kawano Y, Muzuguchi Y, Kumazaki T, Tajiri T. Long-term results of partial splenic artery embolization as supplemental treatment for portal-systemic encephalopathy. *Am J Gastroenterol* 2005; 100: 43-47