



## Evaluation of the effect of partial splenic embolization on platelet values for liver cirrhosis patients with thrombocytopenia

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rate in < 30% and  $\geq$  30% embolization area groups was 50% and 100%, respectively.

**CONCLUSION:** Partial splenic embolization is an effective method to improve platelet values and GPT values in liver cirrhosis patients with thrombocytopenia and the  $\geq$  30% embolization area is meaningful for platelet values improvement. The relationship between the complication rate and embolization area needs further studies.

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**Key words:** Partial splenic embolization; Liver cirrhosis; Thrombocytopenia

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### Abstract

**AIM:** To investigate the effect of partial splenic embolization (PSE) on platelet values in liver cirrhosis patients with thrombocytopenia and to determine the effective embolization area for platelet values improvement.

**METHODS:** Blood parameters and liver function indicators were measured on 10 liver cirrhosis patients (6 in Child-Pugh grade A and 4 in grade B) with thrombocytopenia (platelet values <  $80 \times 10^3/\mu\text{L}$ ) before embolization. Computed tomography scan was also needed in advance to acquire the splenic baseline. After 2 to 3 d, angiography and splenic embolization were performed. A second computed tomography scan was made to confirm the embolization area after 2 to 3 wk of embolization. The blood parameters of patients were also examined biweekly during the 1 year follow-up period.

**RESULTS:** According to the computed tomography images after partial splenic embolization, we divided all patients into two groups: low (< 30%), and high ( $\geq$  30%) embolization area groups. The platelet values were increased by 3 times compared to baseline levels after 2 wk of embolization in high embolization area group. In addition, there were significant differences in platelet values between low and high embolization area groups. GPT values decreased significantly in all patients after 2 wk of embolization. The improvement in platelet and GPT values still persisted until 1 year after PSE. In addition, 3 of 4 (75%) Child-Pugh grade B patients progressed to grade A after 2 mo of PSE. The complication

### INTRODUCTION

The spleen is known to be involved in thrombocytopenia associated with liver cirrhosis<sup>[1]</sup>. Thrombocytopenia in patients with liver cirrhosis has been reported to be caused by an increased platelet pool in the enlarged spleen<sup>[2]</sup>, impaired platelet production in the bone marrow<sup>[3]</sup>, decreased platelet function<sup>[4]</sup>, and abnormalities in the platelet membranes<sup>[5]</sup>. Recently, an article<sup>[6]</sup> reported that decreased production of thrombopoietin (TPO) might also promote the development of thrombocytopenia in liver cirrhosis. Partial embolization of the splenic vessels has been used to treat hypersplenism of thrombocytopenia in liver cirrhosis patients. Mozes *et al*<sup>[7]</sup> described the benefit of partial splenic embolization (PSE) in reducing the prevalence of complications from splenic artery embolization. Miyazaki *et al*<sup>[8]</sup> reported the effectiveness of PSE in thrombocytopenia. Their reports suggested that PSE might be a safe and effective alternative to splenectomy in the treatment of thrombocytopenia. The aim of the current study was to investigate the effect of partial splenic embolization on platelet values in liver cirrhosis patients with thrombocytopenia and to determine

the effective embolization area for platelet values improvement.

## MATERIALS AND METHODS

Ten liver cirrhosis patients with thrombocytopenia (platelet value  $< 80 \times 10^3/\mu\text{L}$ ) were transferred to our department to receive partial splenic embolization at Taipei Medical University Hospital from January 2004 to September 2005. All patients gave informed consent before their participation, and the Ethics Committee of Taipei Medical University Hospital approved the study. The Child-Pugh classifications of these 10 patients were grade A in 6 and grade B in 4 patients. They had no other chronic diseases. Before partial splenic embolization, measurements were taken of platelet, white blood counts, hemoglobin, bilirubin, alkaline phosphatase, and liver function indicators [aspartate aminotransferase, ASAT (GOT), and alanine aminotransferase, ALAT(GPT)].

Before the PSE, they underwent computed tomography (CT, HiSpeed CT/I; GE Medical Systems, Milwaukee, WI, USA) to observe the basal status of the spleen and calculate the volume of the spleen using the software of CT. After 2 to 3 d, angiography and PSE were performed, respectively. A femoral artery approach was used for superselective catheterization of the splenic artery. The catheter tip was placed as distally as possible in either the hilus of the spleen or the intrasplenic artery. Embolization was done by injections of a gelatin sponge (Gelfoam cube, Upjohn, Kalamazoo, USA) cut into 1 to 2 mm cube and suspended in 1 g cefazolin-containing solution. When the blood flow in this artery stopped, we finished the embolization. After 2 to 3 wk of PSE, we did CT scan again to confirm the embolization area via calculating the volume of the spleen. In addition, these patients took antibiotics orally to prevent sepsis. During the one year follow up period, we measured the blood parameters mentioned above biweekly, and recorded the blood parameters at every time point.

### Statistical analysis

Blood parameters were compared using paired *t* test.  $P < 0.05$  means significant differences.

## RESULTS

The mean age of our patients was 56 years (from 19 to 71). According to the embolization areas presented on CT, we divided all patients into two groups: low embolization group ( $< 30\%$ ): 2 patients, and high embolization group ( $\geq 30\%$ ): 8 patients. The average embolization areas in these two groups were 20% and 40%, respectively. The effect of PSE on platelet values is listed in Table 1. In high embolization area group, the platelet values after 2 wk and 1 year of embolization were 2 to 3 times the basal values. In addition, we also evaluated the effect of different embolization areas on platelet values. We observed a marked variation of platelet values between low and high embolization groups. We found that an embolization area equal to or higher than 30% is an effective embolization area for improvement of platelet values.

Table 1 Effects of partial splenic embolization on platelet values

Basal values ( $\times 10^3/\mu\text{L}$ )	Embolization area (%)	After 2 wk ( $\times 10^3/\mu\text{L}$ )	After 1 year ( $\times 10^3/\mu\text{L}$ )
Low embolization			
56	15	69	66
54	25	66	51
Average platelet value		67.5	58.5
High embolization			
60	35	175 <sup>1</sup>	136 <sup>1</sup>
40	45	203 <sup>1</sup>	158 <sup>1</sup>
67	35	258 <sup>1</sup>	140 <sup>1</sup>
61	30	212 <sup>1</sup>	185 <sup>1</sup>
58	30	207 <sup>1</sup>	149 <sup>1</sup>
64	30	71	59
48	50	250 <sup>1</sup>	195 <sup>1</sup>
51	65	159 <sup>1</sup>	141 <sup>1</sup>
Average platelet value		192 <sup>2</sup>	145 <sup>2</sup>

<sup>1</sup>Means significant differences in platelet values between basal values and post-embolization values; <sup>2</sup>Means significant differences in platelet values between low and high embolization areas groups.

Table 2 Effect of partial splenic embolization on GPT values

Basal values (IU/L)	Embolization area (%)	After 2 wk (IU/L)	After 1 year (IU/L)
Low embolization			
145	15	46 <sup>1</sup>	45 <sup>1</sup>
95	25	57 <sup>1</sup>	51 <sup>1</sup>
Average GPT value		51.5	48
High embolization			
87	35	47 <sup>1</sup>	52 <sup>1</sup>
76	45	50 <sup>1</sup>	51 <sup>1</sup>
102	35	54 <sup>1</sup>	40 <sup>1</sup>
98	30	44 <sup>1</sup>	51 <sup>1</sup>
87	30	56 <sup>1</sup>	44 <sup>1</sup>
116	30	58 <sup>1</sup>	54 <sup>1</sup>
79	50	59 <sup>1</sup>	55 <sup>1</sup>
66	65	45 <sup>1</sup>	35 <sup>1</sup>
Average GPT value		52	48

<sup>1</sup>Means significant differences in GPT values between basal values and post-embolization values.

PSE cannot improve the GOT values markedly; however, the GPT values of these 10 patients after 2 wk of PSE decreased baldly and the range of degradation was from 32% to 68% (Table 2). We also found that the improvement of platelet and GPT values still persisted until 1 year after PSE. In addition, 3 of 4 (75%) Child-Pugh grade B patients progressed to grade A after 2 mo of PSE. It suggested that the PSE may improve the liver function with a long-term efficiency. The PSE procedure did not affect other blood parameters.

Regarding complications, there were fever in 10 (100%), pain in 8 (80%) and ascites in 1 (10%) of patients. Ascites occurred in high embolization group. The complication rate in  $< 30\%$  and in  $\geq 30\%$  groups were 50% and 100%, respectively.

## DISCUSSION

In 1973 Maddison<sup>[9]</sup> reported the first case of splenic

artery embolization. In 1979, Spigos<sup>[10]</sup> cured 14 hypersplenism cases using PSE. Since then, PSE has become a major therapy clinically for hypersplenism. The spleen represents one fourth of the total lymphatic mass, serves as a biological filter for the clearance of bacteria and also is essential for rapid antibody production after challenge with blood-borne particulate antigens in the absence of preexisting antibodies<sup>[11]</sup>. In addition, the spleen appears to be the site of production of a nonspecific leukophilic immunoglobulin, tuftsin, that increases the phagocytic activity of polymorphonuclear leucocytes. Thus, it is apparent that the spleen has important and critical functions and its removal is not to be taken lightly<sup>[12]</sup>. Partial splenic embolization represents a potential alternative method to splenectomy when ablation of the splenic parenchyma is desired, particularly in compromised patients, where splenectomy carries significant morbidity and mortality rates. Partial splenic embolization has been successfully used experimentally in the treatment of thrombocytopenia or splenic trauma. Hematologic changes after embolization have been observed, especially in platelet values. There have also been sporadic reports<sup>[13,14]</sup> of successful splenic embolization in humans with thrombocytopenia due to hypersplenism of portal hypertension. Several studies<sup>[15,16]</sup> demonstrated that PSE could not only improve the symptoms of hypersplenism but also could reserve the spleen for immune function maintenance.

A major finding in this study is the effectiveness of PSE in improving platelet values and the extent of embolization seems to be critical in the efficacy of PSE. According to Bruno's study<sup>[17]</sup>, embolization of 50% or less of the splenic mass was almost invariably associated with an elevation of platelet values. In another study<sup>[18]</sup>, the authors demonstrated that 65%-70% embolization area is effectiveness in platelet values improvement in liver cirrhosis patients with thrombocytopenia. In Kimuro's study<sup>[19]</sup>, the platelet counts were improved from  $5.6 \times 10^3/\mu\text{L}$  to  $36 \times 10^3/\mu\text{L}$  in 80% embolization area group and from  $6.2 \times 10^3/\mu\text{L}$  to  $25 \times 10^3/\mu\text{L}$  in 70% embolization area group, which is significantly higher than the former. According to the studies mentioned above, it is suggested that the improved efficacy of PSE on platelet values relates closely to embolization area. In our study, we observed a marked variation of platelet value between low and high embolization groups. We assume that an embolization area equal to or higher than 30% is an effective embolization area for platelet values improvement. Our result is not similar to previous studies. We presume that the limited patient number results in the fact that we cannot differentiate the age, basal platelet values and Child-Pugh classification of patients. Compared to the Bruno and Miyazaki's large-scale studies, there are more variabilities in our study. The various results probably have multiple causes, but patient selection, with different degrees of hepatic insufficiency, is probably of greatest importance.

The complications after PSE include pneumonia, ascites, bleeding, peritonitis, etc. In our study, there were fever in 10 patients, pain in 8 (7 in high embolization and 1 in low embolization) and ascites in 1 (in high

embolization). The complication rate in  $< 30\%$  and in  $\geq 30\%$  groups was 50% and 100%, respectively. In Mukaiya's study<sup>[20]</sup>, they divided all patients into three groups:  $< 50\%$ , 50%-70% and  $\geq 70\%$  according to the embolization area. The complication rate was 28%, 56% and 95%, respectively. In another study<sup>[18]</sup>, the authors also demonstrated that the complication rate associated with the embolization area, which is similar to our study. However, in Hong's study<sup>[21]</sup>, they conducted linear regression analysis between complication rate and embolization area and the correlation coefficient was 0.587. Hong considered that embolization area will affect the complication rate, however, it is not an absolute factor. The relationship between these two parameters needs further study.

Our results showed that the GPT values of these 10 patients after 2 wk of PSE decreased badly and the range of degradation was from 32% to 68%. We also found that the improvement in GPT values persisted until 1 year after PSE. As compared with GPT, GOT is not a specific indicator for liver function. Generally speaking, GOT and GPT values will increase when hepatitis occurs, however, GOT also exists in erythrocytes, cardiac muscles and skeletal muscles. Some extrahepatic diseases, such as myocardial infarction, myocardial necrosis, hemolysis and several muscle related diseases could result in GOT increase. On the contrary, almost all GPT exists in the liver, so that GPT is more specific than GOT for liver function. This is the reason why PSE improved GPT values markedly while there was no effect on GOT values. In addition, 3 of 4 (75%) Child-Pugh grade B patients progressed to grade A after 2 mo of PSE. We suppose that the PSE may be able to improve the liver function, with a long term efficiency. In Noguchi's study<sup>[22]</sup>, 1 liver cirrhosis patient with Child-Pugh grade C progressed to grade B after 6 mo of PSE; 3 of 5 Child-Pugh grade B patients progressed to grade A. In Vujic's study<sup>[23]</sup>, they found liver function improvement in 56 of 128 patients (43.8%) who underwent PSE and their clinical expression included albumin increase and prothrombin formation time abridgement. According to Wang<sup>[24]</sup>, the mechanism by which PSE improves liver function may involve immunologic mechanisms and hemodynamic changes. Noguchi *et al*<sup>[22]</sup> reported that after PSE the changes in the platelet count as compared with the preoperative value negatively correlate with the change in the platelet-associated immunoglobulin G levels. That study suggested that PSE improves the thrombocytopenia induced by immunologic mechanisms in cirrhotic patients. As for hemodynamic mechanisms, Barcena *et al*<sup>[25]</sup> reported that PSE decreased blood flow in the splenic artery and increased blood flow in the hepatic artery and superior mesenteric artery. In addition, Kato *et al*<sup>[26]</sup> found that the decrease in total portal blood flow and the relative increase in the mesenteric blood flow after PSE may decrease liver congestion, enhance the blood supply, and increase the supply of cytokines derived from the digestive tract.

In conclusion, partial splenic embolization is an effective method to improve platelet values in liver cirrhosis patients with thrombocytopenia. We also find that the  $\geq 30\%$  embolization area is meaningful for

platelet values improvement. The relationship between complication rate and embolization area needs further studies.

## COMMENTS

### Background

The spleen is known to be involved in thrombocytopenia associated with liver cirrhosis. Thrombocytopenia in patients with liver cirrhosis has been reported to be caused by an increased platelet pool in the enlarged spleen, impaired platelet production in the bone marrow, a decreased platelet function, and abnormalities in the platelets membranes. Partial embolization of the spleen vessels has been used to treat hypersplenism of thrombocytopenia in liver cirrhosis patients. Studies suggested that PSE might be a safe and effective alternative to splenectomy in the treatment of thrombocytopenia.

### Innovations and breakthroughs

The focus of most previous studies is to evaluate the effectiveness of partial splenic embolization on blood parameters (especially platelets values). The breakthrough of our article is that we found out the efficient embolization area for platelet value improvement, and this provides a meaningful reference for clinic physicians in their therapy.

### Applications

Clinical physicians should adopt the minimal partial splenic embolization area, which could improve the platelet value for treatment of the liver cirrhosis patients with thrombocytopenia. The major advantage is fewer complications after embolization. The  $\geq 30\%$  efficient embolization area shown in our article is multivariate depending on the techniques and patient status; however, we provide another meaningful cerebation for clinical treatment.

### Terminology

PSE: Partial splenic embolization.

### Peer review

This article evaluated the effect of the degree of partial splenic embolisation on platelet values in cirrhotic patients with hypersplenism. The data suggest that at least 30% of the spleen area must be embolisation area in order to increase platelet counts sufficiently.

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