Yonsei Medical Journal
Vol. 44, No. 6, pp. 1053 - 1058, 2003

The Role of Splenectomy in Patients with Hepatocellular Carcinoma and Secondary Hypersplenism

Jae Won Oh, Soo Min Ahn, Kyung Sik Kim, Jin Sub Choi, Woo Jung Lee, and Byung Ro Kim

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea.

Hypersplenism, secondary to portal hypertension, is common in hepatocellular carcinoma (HCC) with liver cirrhosis. Hepatic resection in the patient with hypersplenic thrombocytopenia (HSTC) may cause a perioperative bleeding episode and sometimes, liver failure. In order to investigate the effect of concomitant splenectomy in HCC patients with HSTC, clinical parameters are retrospectively reviewed for 18 HCC patients who underwent hepatic resection with or without splenectomy.

Among 581 HCC patients who underwent hepatic resection during the past 17 years, 18 patients with HSTC were investigated. Twelve of them underwent hepatic resection for HCC and had a concomitant splenectomy and the remaining 6 patients underwent hepatic resection for HCC only. The clinical outcomes and postoperative changes in platelet count, serum albumin level, serum total bilirubin levels, prothrombin time and clinical staging (Child-Pugh Classification) were reviewed.

The resected spleen mean weight was 350.7 ± 102.9 g. Postoperative platelet counts were significantly increased with albumin levels and clinical staging scores also improved after the splenectomy. Among the 12 patients who had a splenectomy, 6 patients had postoperative complications and one died of recurrent variceal bleeding.

According to this data, it is not harmful to perform a concomitant splenectomy and hepatectomy for the HCC patient with severe HSTC, it can even be beneficial in improving both the platelet count and clinical staging.

Key Words: Splenectomy, hepatectomy, hypersplenic thrombocytopenia (HSTC), hepatocellular carcinoma (HCC)

INTRODUCTION

A large number of patients with hepatocellular carcinoma (HCC) also have concurrent liver disease such as cirrhosis. Some of these patients with liver cirrhosis usually have thrombocytopenia caused by portal hypertension and secondary hypersplenism. Thrombocytopenia secondary to hypersplenism is the result of sequestration of platelets in the splenic reticuloendothelial system and decompression of portal pressure may not improve the thrombocytopenia.

The lack of established treatment guidelines for hypersplenism and the uncertain effects of splenectomy on the immune system of patients with malignant tumors,[1,2] make it difficult for surgeons to treat HCC patients with hypersplenism.[3-5] Hypersplenic thrombocytopenia (HSTC) is defined as, thrombocytopenia secondary to splenic congestion with platelet counts that are usually less than 10,000/mm^3. The incidence of HSTC among liver cirrhosis patients is reported to be between 11% and 33%.[6-8] Hepatic resection in HCC patients with HSTC is a very risky procedure due to impaired liver function, coagulopathy and a bleeding tendency during surgery.[9,10] Even though splenectomy is not generally recommended, unless the patient is actually suffering from thrombocytopenia, splenectomy in HCC patients with HSTC has been reported to be effective in improving platelet counts and decreasing the severity of coagulopathy.[7,8] However, portal vein thrombosis and impaired immune function, such as in post splenectomy syndrome, are potential side effects.[7,11,12] The aim of this study, therefore, was to assess the value of concurrent splenectomy in the treatment of HCC patients with HSTC.

Received October 10, 2003
Accepted October 28, 2003

Reprint address: requests to Dr. Jin Sub Choi, Department of Surgery, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-361-5569, Fax: 82-2-313-8289, E-mail: choi5491@yumc.yonsei.ac.kr

MATERIALS AND METHODS

Patients

Five hundred and eighty-one patients underwent hepatic resection for HCC at Severance Hospital, Yonsei University Medical Center, between March 1986 and July 2003. Of these 581 patients, 18 HCC patients who were also diagnosed with cirrhosis of the liver and HSTC, were retrospectively selected for the study. Twelve of them underwent hepatic resection with splenectomy (splenectomy group; S) and the others underwent only hepatic resection (No splenectomy group; NS). All 18 patients had preoperative liver function tests, an indocyanine-green (ICG) clearance test, abdominal ultrasound (US), computed tomography (CT) and angiography. Characteristics of the 18 selected patients are shown in Table 1.

Methods

Under general endotracheal anesthesia, all 18 patients underwent hepatic resection but concomitant splenectomy was performed before the hepatic resection in only 12 patients. Intraoperative platelet transfusion was started upon skin incision with a target platelet count of 100,000/mm^3. Platelet transfusion was continued until the end of the splenectomy in the splenectomy patients. The Pringle maneuver was performed as necessary during hepatic resection. Complete blood count (CBC), serum chemistry studies, and prothrombin time were measured on the seventh day postoperatively. The measured values were compared to preoperative values for analysis. Operative morbidity and mortality were defined as those occurring within one month after surgery.

Statistics

Statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS, Inc., Chicago, IL, USA). Preoperative and postoperative platelet counts, albumin levels, bilirubin levels and prothrombin time were compared using the Wilcoxon signed ranks test. A p value < 0.05 was considered statistically significant.

RESULTS

Histopathologic studies showed evidence of liver cirrhosis, aside from hepatocellular carcinoma, in all 18 patients. The malignant lesion(s) was (were) located in the right lobe in 6 patients and in the left lobe in 6 patients in group S. In the NS group, malignant lesion(s) was (were) located in the right lobe in 4 patients and in the left lobe in 2 patients. The average size of the tumor was 4.04 cm (range: 1.5 - 8.0) in group S and 4.94 cm (range: 2.2 - 9.0) in group NS. The average number of lesions was 1.4 (range: 1 - 3) in group S and 1.5 (range: 1 - 4) in group NS (Table 2). The average weight of the resected spleens was

Table 1. Demographic of Patients

	Splenectomy (+) (n=12)	Splenectomy (-) (n=6)	p value
Gender (male: female)	9:03	4:02	ns
Age (years)	48.8 (range: 37-61)	58.7 (range: 52-68)	<0.05
Serum HBs Ag (+)	11	4	ns
ICG R15 (%)	16.5 ± 6.9 (range: 7.1-25.2)	15.0 ± 9.8 (range: 3.5-32.1)	ns
Child-Pugh classification			ns
A	6	4	
B	6	2	

HBs Ag, hepatitis B surface antigen; ICG, indocyanine green; ns, not significant.

Table 2. Details Regarding Tumors

	Splenectomy (+) (n=12)	Splenectomy (-) (n=6)	*p* value
Number	1.4 (range: 1-3)	1.5 (range: 1-4)	ns
Maximum size (cm)	4.0 (range: 1.5-8.0)	4.9 (range: 2.2-9.0)	ns
Distribution			ns
Left lobe	6	4	
Right lobe	6	2	

ns, not significant.

350.67 ± 102.86 g (range 166-470). All the resected spleens showed evidence of congestion. In terms of hepatic resection, a wedge resection, 6 segmental resections, 2 left lobectomies, and 3 right lobectomies comprised the S group surgery, with 2 wedge resections, a segmentectomy, a left lobectomy and a right lobectomy for the NS group. Details of the surgery are as in Table 3.

Estimated blood loss during surgery was 1625 ± 976.19 ml (range 400 - 3200 ml) in the S group and 1068.3 ± 918.7 ml (range: 400 - 2250 ml) in the NS group (p=ns: not significant). The average amount of intraoperative transfusion (plasma and packed red cells) was 1295 ± 1057.78 ml in the S group and 1195.0 ± 1250.3 ml in the NS group (p=ns). No transfusion was necessary for 2 patients of the S group and one patient of the NS group. The average preoperative platelet count was $55.25\times10^3 \pm 14.59\times10^3/mm^3$ and the average postoperative platelet count was $176.83 \times 10^3 \pm 46.49\times10^3/mm^3$ in the S group, but were $79.00 \times10_3 \pm 33.17\times10^3/mm^3$ and $73.83\times10^3 \pm 26.43 \times10^3/mm^3$ in the NS group, respectively. All patients of the S group showed improvement in their platelet counts by 100,000/mm^3 or more on postoperative day #7. The increase in platelet count after splenectomy was statistically significant ($p<0.0001$). Albumin levels also improved from preoperative levels of 3.0 ± 0.3g/dl to postoperative levels of 3.4 ± 0.3 g/dl in the S group, while those levels in the NS group were 3.6 ± 0.6 g/dl and 3.4 ± 0.3 g/dl, respectively (p=0.015). The mean prothrombin time (INR) of the S group increased from 1.18 ± 0.12 preoperatively to 1.56 ± 0.50 at POD #7, and that of the NS group also increased from 1.07 ± 0.12 preoperatively to 1.20 ± 0.13 at POD #7. (p=0.01). The mean serum bilirubin levels increased from 1.22 ± 0.66 mg/dl to 1.36 ± 0.86 mg/dl in the S group, and from 1.28 ± 0.89 mg/dl to 1.91 ± 2.01 mg/dl in the NS

Table 3. Surgical Details

	Splenectomy (+) (n=12)	Splenectomy (-) (n=6)	*p* value
Operation			ns
Wedge resection	1	2	
Segmentectomy	6	1	
Lobectomy (right: left)	3 : 2	2 : 1	
Operation time (min)	273.3 ± 87.6	235.0 ± 74.1	ns
Blood loss (ml)	1625.0 ± 976.2	1068.3 ± 918.7	ns
FFP and packed RBC transfusion (ml)	1295.0 ± 1057.8	1195.0 ± 1250.3	ns
Weight of removed spleen (gram)	350.7 ± 102.9		

FFP, fresh frozen plasma; ns, not significant.
Values were shown as mean ± SEM.

group, (p=ns). However, 9 out of the 12 patients in the S group showed a decrease in serum bilirubin levels postoperatively but 5 patients of the NS group showed an increase in serum bilirubin levels. 4 out of 6 Child-Pugh class B patients in the S group showed clinical improvement at POD #7 and were re-classified as Child-Pugh class A, but no patients in the NS group showed improvement of Child-Pugh classification at POD #7. Laboratory study values are summarized in Table 4.

One patient in the S group died 20 days after surgery due to hepatic failure secondary to recurrent bleeding from esophageal varices. One patient in the NS group died of hepatic failure at POD #26. There were six complications in the S group. One patient had an upper gastrointestinal bleeding postoperatively, which was treated successfully via EGD. Four patients had postoperative pleural effusion and one patient underwent laparotomy for a perforated peptic ulcer after splenectomy. All six patients of the NS group showed postoperative pleural effusion, which was well controlled, and one patient with Child-Pugh class B suffered esophageal varices bleeding which was controlled by endoscopic band ligation.

DISCUSSION

Both morbidity and mortality after hepatic resection have decreased in recent years, due to advances in surgical techniques and perioperative care.[13-16] However, hepatic resection for HCC patients with concurrent HSTC remains complicated and challenging. This study demonstrated that splenectomy increases platelet counts in HCC patients with hypersplenism. Increased platelet counts, in turn, decrease the risk of bleeding during hepatic resection. Changes in albumin levels and prothrombin time were also noted in this study, but their significance is uncertain due to postoperative transfusion and albumin supplementation. Hyperbilirubinemia secondary to hypersplenism is thought to be due to increased destruction of red blood cells, and causes significant strain on the liver's ability to process bilirubin.[17] Splenectomy aids in decreasing bilirubin levels, although its mechanism is still uncertain. Conservative treatment to help liver function recovery also decreases bilirubin levels. Generally, serum bilirubin levels increase temporarily after hepatic resection.[18,19] Nine patients in S group experienced decrease in serum bilirubin levels but 3 patients in the S group and 5 patients of the NS group had elevated bilirubin levels, compared to preoperative values, even on postoperative day number 7. Serum bilirubin levels had decreased to preoperative levels in 3 patients of the S group when they were retested one month after surgery but only 2 patients in the NS group reached preoperative levels in that time.

Transcatheter partial splenic artery embolization (PSE) has been reported to be effective in treating portal hypertension and hypersplenism.[20]

Table 4. Comparison of Clinical Laboratory Study Details

Clinical parameters	Splenectomy	Before surgery	1 week after surgery	p value
Platelet count ($\times 10^3/mm^3$)	(+)	55.25 ± 14.59	176.83 ± 46.49	<0.0001
	(-)	79.00 ± 33.17	73.83 ± 26.43	
Albumin (g/dl)	(+)	3.0 ± 0.3	3.4 ± 0.3	0.015
	(-)	3.6 ± 0.6	3.4 ± 0.3	
Prothrombin Time (INR)	(+)	1.18 ± 0.12	1.56 ± 0.50	0.01
	(-)	1.07 ± 0.12	1.20 ± 0.13	
Bilirubin (mg/dl)	(+)	1.22 ± 0.66	1.36 ± 0.86	0.885
	(-)	1.28 ± 0.89	1.91 ± 2.01	

Values were shown as mean ± SEM.

Hirai and colleagues reported good results after treating 11 patients suffering from hypersplenism using PSE[21] and Sangro, et al. reported treating 40 HCC patients, who suffered spontaneous bleeding due to decreased platelet count, using PSE before interferon treatment or chemotherapy for unresectable HCC.[5] However, some studies indicate that splenic artery embolization cannot effectively decrease total bilirubin levels.[5,21-24] It is also difficult to expect splenic embolization alone, to treat hypersplenism effectively enough, to improve bilirubin levels. Moreover, splenic embolization can cause serious complications such as splenic abscess, splenic rupture and hepatorenal syndrome[24] with complication rates ranging from 30% to 40% and mortality rates ranging from 20% to 30%.[25]

Some studies report that the spleen prevents hepatic injury, caused by endotoxin release during hepatic resection, by controlling the levels of cytokines involved in the inflammatory reaction,[26] and that it also suppresses hepatic regeneration.[27] Takayama, et al. reported that splenectomy improved hepatic synthetic function[17] and, in other experimental and clinical trials, have also reported that splenectomy enhances hepatic regeneration after hepatic resection.[28,29] Some patients in the S group showed improvements of Child-Pugh classification after splenectomy. The exact causes are not certain but transfused blood products with albumin during and after surgery, may improve laboratory findings. Also, increased portal blood flow after splenectomy may also impact on liver regeneration.[17,28,29]

Our results indicate that splenectomy increases platelet counts and hence makes hepatic resection for HCC patients with HSTC safer.

In conclusion, concomitant splenectomy prior to hepatic resection is a safe procedure for the HCC patient who has liver cirrhosis and secondary hypersplenism.

REFERENCES

1. Hellstrom KE, Sjogren HO, Warner GA. Serum factor in tumor-free patients canceling the blocking of cell-mediated tumor immunity. Int J Cancer 1971;8:185-91.
2. Klein WJ Jr. Effect of spleen cells on cytotoxicity by immune lymph node cells: cell-mediated immune suppression enhancement *in vitro*. J Immunol 1972;109: 51-8.
3. Soper NJ, Rikkens LF. Effect of operations for variceal hemorrhage on hypersplenism. Am J Surg 1982;144: 700-3.
4. Khishen MA, Henderson JM, Millikan WJ Jr. Kutner MH, Warren WD. Splenectomy is contraindicated for thrombocytopenia secondary to portal hypertension. Surg Gynecol Obstet 1985;160:233-8.
5. Sangro B, Bilbao I, Herrero I, Corella C, Longo J, Beloqui O, et al. Partial splenic embolization for the treatment of hypersplenism in cirrhosis. Hepatology 1993;18:309-14.
6. Yu MW, Hsu FC, Sheen IS, Chu CM, Lin DY, Chen CJ, et al. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. Am J Epidemiol 1997;145:1039-47.
7. Morali GA, Blendis LM. Splenomegaly in portal hypertension: cause and effects. In: Okuda K, editor. Portal hypertension-clinical and physiological aspects. 1st ed. Tokyo: Springer-Verlag; 1993. p.85-99.
8. Soper NJ, Rikkers LF. Effects of operations for variceal hemorrhage on hypersplenism. Am J Surg 1982;144: 700-3.
9. Capron JP, Chivrac D, Dupas JL, Remond A, Ossart JL, Lorriaux A. Massive splenic infarction in cirrhosis: report of a case with spontaneous disappearance of hypersplenism. Gastroenterology 1976;71:308-10.
10. Lokich J, Costello P. Splenic embolization to prevent dose limitation of cancer chemotherapy. AJR 1983;140: 159-61.
11. Miller EM, Hagedorn AB. Result of splenectomy. A follow-up study of 140 consecutive cases. Ann Surg 1951;143:815-21.
12. Krivit W, Geibing GS. Overwhelming postsplenectomy infection. Surg Clin North Am 1079;59:223-33.
13. Kosuge T, Makuuchi M, Takayama T, Yamamoto J, Shimada K, Yamasaki S. Long-term results after resection of hepatocellular carcinoma: experience of 480 cases. Hepato-gastroenterology 1993;40:328-32.
14. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a Western experience. World J Surg 1986;10:311-7.
15. Sasaki Y, Imaoka S, Masutani S, Ohashi I, Ishikawa O, Koyama H, et al. Influence of coexisting cirrhosis on long-term prognosis after surgery in patients with hepatocellular carcinoma. Surgery 1992;112:515-21.
16. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298-304.
17. Takayama T, Makuuchi M, Yamazaki S, Hasegawa H. The role of splenectomy in patients with hepatocellular carcinoma and hypersplenism as an aid to hepatectomy [in Japanese with an English abstract]. J Jpn Surg Soc 1989;90:1043-8.
18. Makuuchi M, Mori T, Gunven P, Yamazaki S, Hasegawa H. Safety of hemihepatic vascular occlusion during resection of the liver. Surg Gynecol Obstet 1987;

164:155-8.
19. Wu CC, Hwang CR, Liu TJ, P'eng FK. Effects and limitations of prolonged intermittent Ischemia for hepatic resection of the cirrhotic liver. Br J Surg 1996; 83:121-4.
20. Papadimitriou J, Tritakis C, Karatzas G. Treatment of hypersplenism by embolus placement in the splenic artery. Lancet 1976;2:1268-70.
21. Hirai K, Kawazoe Y, Yamashita K, Kumagai M, Tanaka M, Sakai T, et al. Transcatheter partial splenic arterial embolization in patients with hypersplenism: a clinical evaluation as supporting therapy for hepatocellular carcinoma and liver cirrhosis. Hepato-gastroenterology 1986;33:105-8.
22. Sakata K, Hirai K, Tanikawa K. A long-term investigation of transcatheter splenic arterial embolization for hypersplenism. Hepato-Gastroenterology 1996;43:309-18.
23. Mukaiya M, Hirata K, Yamashiro K, Katsuramaki T, Kimura H, Denno R. Changes in portal hemodynamics and hepatic function after partial splenic embolization (PSE) and percutaneous transhepatic obliteration (PTO). Cancer Chemother Pharmacol 1994;33 Suppl:S37-41.
24. 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;2:125-7.
25. Trojanowski JQ, Harrist TJ, Athanasoulis CA, Greenfield AJ. Hepatic and splenic infarctions: complications of therapeutic transcatheter embolization. Am J Surg 1980;139:272-7.
26. Suzuki S, Nakamura S, Serizawa A, Sakaguchi T, Konno H, Muro H, et al. Role of Kupffer cells and the spleen in modulation of endotoxin-induced liver injury after partial hepatectomy. Hepatology 1996;24:219-25.
27. Tomikawa M, Hashizume M, Higashi H, Ohta M, Sugimachi K. The role of the spleen, platelets and plasma hepatocyte growth factors activity on hepatic regeneration in rats. J Am Coll Surg 1996;182:12-6.
28. Ohira M, Umeyama K, Taniura M, Yamashita T, Morisawa S. An experimental study of a splenic inhibitory factor influencing hepatic regeneration. Surg Gynecol Obstet 1987;164:438-44.
29. Sato K, Tanaka M, Tanikawa K. The effect of spleen volume on liver regeneration after hepatectomy--a clinical study of liver and spleen volumes by computed tomography. Hepato-Gastroenterology 1995;42:961-5.