

Reversal of Hypersplenism Following Orthotopic Liver Transplantation

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The purpose of this study was to clarify the effect of orthotopic liver transplantation on hypersplenism. In a 1-year period from July 1, 1986 to June 30, 1987, 196 adult patients underwent 233 orthotopic liver transplantations. Of the 58 patients with hypersplenism who were analyzed in this study, hypersplenism was more commonly associated with postnecrotic cirrhosis than other kinds of liver disease (55.3% (47/85) vs. 14.5% (11/76); $p < 0.001$). Postoperative platelet counts were statistically higher than preoperative values ($p < 0.05$). The latest platelet counts were more than 100,000/mm³ in 53 patients (91.4%). Of the eight patients whose preoperative and postoperative spleen volumes could be compared, all showed the reduction in the spleen size ($p < 0.02$). We conclude that orthotopic liver transplantation, which is a radical surgical procedure for portal hypertension, reverses hypersplenism.

controversial.¹⁻⁹ Orthotopic liver transplantation (OLTx), which has become an accepted modality of treatment for end-stage liver disease,^{10,11} is a radical surgical procedure for portal hypertension. The purpose of this study was to evaluate the effect of OLTx on hypersplenism.

Patients and Methods

HYPERSPLENISM IS FREQUENTLY ASSOCIATED with liver cirrhosis, which commonly presents itself as splenomegaly with hematologic disorders, i.e., leukopenia, thrombocytopenia, and anemia.¹ The incidence of hypersplenism among cirrhotics varies from 15% to 70%,¹ and splenectomy is known to relieve the hematologic disorders associated with this clinical entity.²⁻⁴ Passive congestion of the spleen due to portal hypertension is thought to cause the splenomegaly, which results in the sequestration and the destruction of the blood elements.^{5,6} Although portacaval and distal splenorenal shunts are known to reduce the splenic vein pressure, the effect of these shunts on hypersplenism remains

In a 1-year period between July 1, 1986 and June 30, 1987, 196 adult patients underwent 232 orthotopic liver transplantations (OLTx) at the Presbyterian University Hospital of Pittsburgh, University of Pittsburgh. Their ages ranged from 19 to 76 years, with a mean of 44.9 years; 85 patients were men (43.4%). The indications for OLTx consisted of postnecrotic cirrhosis in 101 patients, (21 alcoholic, 80 nonalcoholic), primary biliary cirrhosis in 41, primary sclerosing cholangitis in 20, neoplasm in 10, and other indications in 24 patients. Sixty-three of these patients (32.1%) demonstrated evidence of hypersplenism, as indicated by leukocyte counts of less than 5000/cmm and/or platelet counts of less than 100,000/cmm, and had follow-up periods of more than 3 months. The age among these patients varied from 21 to 76 years, with a mean of 45.6, and 34 were men (54%). The indications for OLTx were postnecrotic cirrhosis in 47 patients (10 alcoholic, 37 nonalcoholic), primary biliary cirrhosis in 5, primary sclerosing cholangitis in 4, neoplasm with postnecrotic cirrhosis in 1, and other indications in 6 patients. Follow-up periods ranged from 133 to 547 days, with a mean of 355 days. Three of these patients developed pathologic thrombocytopenia: aplastic anemia, idiopathic

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thrombocytopenic purpura, and systemic cytomegalovirus infection, respectively. These patients, as well as two other patients who underwent interferon treatment for the prevention of recurrent hepatitis B, were excluded from the investigation of the change in the platelet counts. The remaining 58 patients were analyzed in this study. The immunosuppressive regimen consisted of Cyclosporin and corticosteroids. Steroid-resistant rejection was treated with Orthoclone OKT®3 (Ortho Pharmaceutical Co., Raritan, NJ).

Serial platelet counts were obtained from the charts on postoperative days 7, 14, 21, and 30. The most recent platelet counts were acquired from the outpatient clinic or from the family physicians. Postoperative leukocyte counts were not evaluated because of the effect of postoperative immunosuppression on the peripheral leukocyte counts.

In 8 patients with hypersplenism, the spleen volume was measured from computed tomograms (CT) taken before and 22 to 80 days after operation, with a mean of 41 days after OLTx; these measurements were used for comparison of changes in spleen size.

Paired Student's and Chi-square tests were used in the statistical evaluation in this study.

Results

Table 1 lists the incidence of hypersplenism in relation to indications for OLTx among patients who underwent OLTx and had follow-up periods of more than 3 months. The incidence of hypersplenism was significantly higher in patients with end-stage liver disease due to postnecrotic cirrhosis, either alcoholic or nonalcoholic in etiology ($p < 0.001$, $X^2 = 29.08$).

Table 2 lists the changes in the platelet counts in different categories. The patients with postnecrotic cirrhosis, either alcoholic or nonalcoholic, demonstrated statistically significant increases beginning with postoperative day 14 ($p < 0.05$ or less). In the patients with primary biliary cirrhosis, a statistically significant difference was observed

TABLE 1. Indications for Orthotopic Liver Transplantation and the Incidence of Hypersplenism

Indication	Patients	
	Total	With Hypersplenism
Postnecrotic cirrhosis†	85	47 (55.3%)
Alcoholic	16	9 (56.3%)
Nonalcoholic	69	38 (51.1%)
Primary biliary cirrhosis‡	36	5 (13.9%)
Others‡	40	6 (15%)
Primary sclerosing cholangitis	18	3 (16.7%)
Tumor	8	2* (25%)
Fulminant hepatitis	5	0
Alpha-1-antitrypsin deficiency	4	1 (25%)
Hemochromatosis	2	0
Wilson's disease	1	0
Others	2	0
Total	161	58 (36%)

* Both patients had associated liver cirrhosis.
 $p < 0.001$ ($X^2 = 29.08$) when the incidence of hypersplenism was compared between † and ‡

between the preoperative and the current platelet counts ($p < 0.05$). In patients with other diseases, statistical differences from the preoperative platelet counts were observed on postoperative day 14. Overall, as shown in Figure 1, the increase in platelet counts after OLTx in patients with hypersplenism was statistically significant. The platelet counts on postoperative days 7, 14, 21, 30, and the current or last platelet counts were significantly higher than the preoperative values ($p < 0.05$, 0.001, 0.001, 0.001, and 0.001, respectively). The latest platelet counts are more than 100,000/mm³ in all but five patients (91.4%).

Table 3 lists the changes in the spleen size after OLTx with the use of CT in eight patients with hypersplenism. All patients showed the reduction in the spleen volume, 7% to 50%, with a mean of 23.1%, which was a statistically significant volume reduction as compared to the preoperative spleen size ($p < 0.02$).

TABLE 2. Changes in Platelet Counts Following Orthotopic Liver Transplantation in Patients with Hypersplenism

Indications	Platelet Counts (/mm ³)					
	Preoperative	Postoperative Day				
		7	14	21	30	Current
PNC-A (n = 9)	69 ± 26	73 ± 46	234 ± 123†	193 ± 79‡	152 ± 58‡	216 ± 156*
PNC-NA (n = 38)	63 ± 17	72 ± 38	185 ± 101‡	176 ± 99	164 ± 84	168 ± 72
PBC (n = 5)	87 ± 7	120 ± 65	240 ± 247	218 ± 137	242 ± 153	224 ± 117*
Others (n = 6)	79 ± 16	119 ± 79	232 ± 145*	197 ± 125	198 ± 164	271 ± 215

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.005$ and ^{||} $p < 0.0001$ when compared to preoperative values (paired Student's t-test); PNC-A, postnecrotic cir-

rhosis, alcoholic; PNC-NA, postnecrotic cirrhosis, nonalcoholic; PBC, primary biliary cirrhosis.

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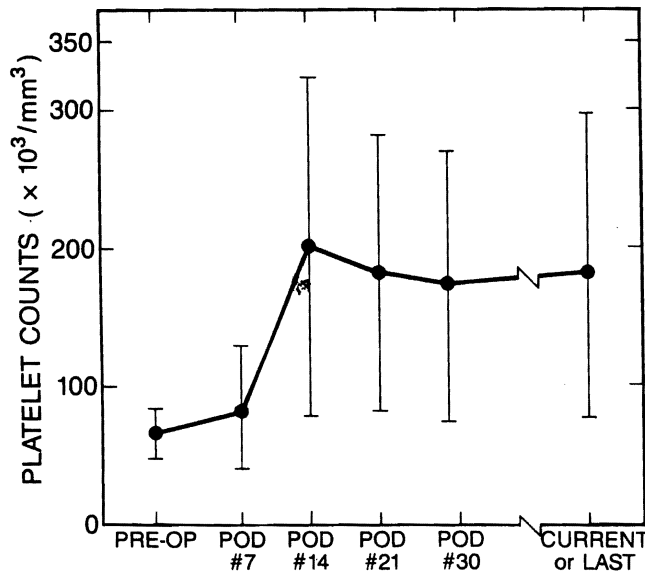


FIG. 1. Changes in platelet counts after orthotopic liver transplantation for hypersplenism. Platelet counts on postoperative days 7, 14, 21, 30, and the recent counts are statistically higher than preoperative values ($p < 0.05, 0.001, 0.001, 0.001, 0.001$, respectively). POD = postoperative day.

Discussion

The effect of portasystemic or selective shunt procedures on hypersplenism remains controversial. For portacaval shunts, Sullivan et al.² in 1961 and Mitchnick et al.¹ in 1980 showed no consistent effect on hypersplenism, whereas Morris et al.⁵ in 1962 and Felix et al.⁷ in 1974 showed persistent correction of hypersplenism, as judged by the reduction in the spleen size and the correction of the hematologic disorders, in 4 of 8 and 5 of 13 patients, respectively. For distal splenorenal shunts, Vang et al.⁸ in 1976 reported no significant change in the platelet counts, whereas Hutson et al.⁶ in 1977 and Ferrara et al.⁹ in 1979

reported a relief of hypersplenism in the majority of patients, as judged by the improvement of the leukocyte and the platelet counts. Also, reports by Puttini et al.³ in 1979 and by Soper et al.⁴ in 1982, which consisted mainly of portasystemic shunts and distal splenorenal shunts, respectively, showed the improvement of the hematologic disorders and, in the latter, decreased spleen size after the shunt procedures.

Our study demonstrates a dramatic effect of OLTx on hypersplenism, as judged by the changes in the platelet counts and the spleen size after OLTx. Thrombocytopenia immediately after OLTx is a common phenomenon due to the platelet sequestration and the destruction in the liver allograft,¹² but our data show that the platelet counts reach a plateau 2 weeks after OLTx and then remain stable thereafter.

The increase in the postoperative platelet counts following OLTx in this series were statistically more significant in patients with postnecrotic cirrhosis, which may be due to the limited number of the patients with other diseases. However, the incidence of hypersplenism was undoubtedly higher among the patients with postnecrotic cirrhosis, either alcoholic or nonalcoholic, as compared to other diseases.

The development of hypersplenism in liver cirrhosis has been attributed to splenic congestion.^{5,6} However, other factors such as splenic stimulation from gut-derived antigens due to spontaneous portasystemic shunting^{13,14} have been implicated as a cause, which may explain the inconsistent effect of shunt procedures on hypersplenism. In general, more collaterals are encountered during OLTx for postnecrotic cirrhosis, as compared to other diseases, such as primary biliary cirrhosis or sclerosing cholangitis. By replacing a cirrhotic liver in the end stage with a non-cirrhotic allograft, OLTx not only reduces the portal pressure but also obliterates the collateral circulation, either surgically during OLTx or spontaneously after the reduc-

TABLE 3. Comparison of Spleen Size Before and After Orthotopic Liver Transplantation in Patients with Hypersplenism

Case	Liver Disease	Spleen Volume (cc ³)		% Changes
		Preoperative*	Postoperative*	
1	PNC-A	753	685 (80)†	-9
2	PNC-NA	1670	1029 (22)†	-38
3	PNC-NA	699	596 (23)†	-15
4	PNC-NA	595	515 (48)†	-13
5	PNC-NA	951	470 (34)†	-50
6	PNC-NA	1863	1166 (31)†	-37
7	PNC-NA	888	831 (32)†	-7
8	PBC	1912	1605 (60)†	-16
mean ± S.D.		1166 ± 552	861 ± 387	-23.1 ± 16.1

* $p < 0.02$ (paired Student's t-test); () †, number of postoperative days; PNC-A, postnecrotic cirrhosis, alcoholic; PNC-NA, postnecrotic

cirrhosis, nonalcoholic; PBC, primary biliary cirrhosis.

tion of the portal pressure. The degree of collateral formation due to portal hypertension may play a role in the development of hypersplenism.

Although the exact pathogenesis of hypersplenism remains to be elucidated, this series demonstrated that OLTx seems to reverse hypersplenism.

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