Portal Systemic Shunt for Portal Hypertension: Importance of Bromsulphalein Retention for Prediction of Survival

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ADEQUATE reserve of liver function is the major factor which influences the survival of patients with hepatic cirrhosis and portal hypertension, unless uncontrollable bleeding from esophageal varices *per se* is a problem. Since Blakemore, Lord and Whipple first applied portacaval and splenorenal shunt to the therapy of bleeding esophageal varices in 1945, numerous reports have confirmed the effectiveness of a portasystemic shunt in preventing recurrent hemorrhage from varices in patients who have previously bled. But increasing experience has indicated that encephalopathy and late hepatic failure was remarkable following either therapeutic or prophylactic portasystemic shunts.

There is great need for an accurate estimation of hepatic reserve in liver cirrhosis and portal hypertension to determine the tolerance to survive portasystemic shunt without complication of hepatic failure. The author has approached this problem by statistical analysis of those patients who underwent portasystemic shunt to prevent death from rupture of bleeding eosphageal varices, using a group of patients treated by splenectomy as control. The present study questions the effect of late hepatic failure after portasystemic shunt and its relation to survival.

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Material

All patients in this series were operated upon at National Taiwan University Hospital from 1956 through 1970. Sixty-one patients underwent splenectomy and 48 patients were treated by portal systemic shunt (Table 1). Patients who were operated upon had esophageal varices demonstrable by esophagoscopy, contrast medium esophagogram or by splenoportography, but not necessarily those who had variceal bleeding. That is, 19 of 61 patients in the splenectomy group and eight of 48 patients in the shunt group were operated upon prophylactically. Three of 48 patients in the shunt group who had splenectomies, later underwent mesocaval shunt because of recurrent esophageal variceal bleeding. Eight patients underwent construction of portacaval shunt, six were end-to-side procedures and two were side-to-side. Splenorenal shunts were constructed in 24 patients and mesocaval shunts were performed in 17 patients. One patient with portacaval end-to-side shunt later underwent mesocaval shunt because of bleeding 2 years after the first shunt which thrombosed soon after operation. No particular criteria was elicited for selection of patients for either splenectomy or portasystemic shunt. The preliminary chi-square tests of age distribution (Table 2), hepatic functional reserve by Child's classification [6]

TABLE 1. *Method of Surgical Treatment for Portal Hypertension*

Splenectomy	64*1		
Portal systemic venous shunt	49		
Splenorenal shunt		24	
Portacaval shunt		8*2	
End-to-side			6
Side-to-side			2
Mesocaval shunt		17	

*1 Three patients later needed mesocaval shunts for recurrent variceal hemorrhage 2 and 4 years after splenectomy.

*2 One patient underwent mesocaval shunt because of bleeding 2 years after portacaval shunt which thrombosed.

TABLE 2. *Age Distribution of 61 Patients Treated by Splenectomy and 48 Patients Treated by Portasystemic Shunt*

Age (yr.)	Splenectomy	Portasystemic Shunt
1–10	2	2
11–20	3 (15)	0 (8)
21–30	10	6
31–40	25	15
41–50	14	20
51–60	7	5
	61	48

Chi-square = 4.5373, Probability > 0.1, d.f. = 3.

(Table 3) and types of hepatic disease (Table 4) indicated that there were no significant differences between the two groups. Therefore, the two groups were considered to be sufficiently similar to permit a conclusion by comparison of results.

Results

Operative Mortality. Postoperatively, there were six deaths in the splenectomy group and five in the shunt group. These patients died in the hospital within 40 days after operation. In the splenectomy group, one patient died of hemorrhagic shock on the 3rd postoperative day. One patient died of cerebrovascular accident with coma on the 40th day after splenectomy. The remaining four splenectomized patients died of variceal rupture after operation. In the shunt group, one patient died of shock due to nonvariceal bleeding on the 4th postoperative day. Two patients died of variceal hemorrhage, in one at autopsy, the shunt was found thrombosed due to compression by the duodenum on the inferior vena cava which constructed the mesocaval shunt. In the other two patients, one with a mesocaval shunt and the other with a side-to-side portacaval shunt, hepatic failure developed and they died on the 12th and 14th day after operation, respectively.

Survival. Ninety-eight patients survived the operation and have been followed from 3 months to 15 years. The cumulative survival rate was computed by the life table method [8] year by year. The survival rates in the splenectomy and the shunt group are represented in Tables 5 and 6, respectively. The survival rates at the interval of 6–7 years were compared between the two groups. The chi-square value of the difference in the survival was computed as 0.2166, indicating that there was no significant difference ($p > 0.1$) in the cumulative survival rates between the shunt and the splenectomy group. This fact was also assured by comparing the two groups, of which the standard error of cumulative survival rate showed much overlapping. Therefore, it is concluded that the cumulative survival rate of the splenectomy and the shunt group is insignificantly different.

Cause of Deaths. Including the operative deaths, nineteen patients in the splenec-

TABLE 3. *Classification of Patients According to Child's Group of Hepatic Functional Reserve*[6]

Child's Group	Splenectomy	Portasystemic Shunt
A	41	30
B	14 (20)	15 (18)
C	6	3
	61	48

Chi-square = 0.0959, Probability > 0.1, d.f. = 1.

tomy group and 14 in the shunt group died (Table 7). Twelve of 19 patients in the splenectomy group and three of 14 in the shunt group died of esophageal variceal bleeding. The significant difference ($p < 0.05$) between the two groups in the frequency of deaths from hemorrhage indicated that portasystemic shunt was more effective in preventing hemorrhage from esophageal varices than splenectomy. Among 14 deaths in the shunt group, eight patients died of hepatic failure. This is quite a contrast to the splenectomy group, in which only two of 19 patients died of hepatic failure. The difference was very significant statistically ($p < 0.025$). Table 7 indicates that shunt procedure prevent hemorrhage, but death from hepatic failure occurs more frequently.

Bromsulphalein (BSP) Retention and Survival Days. The preoperative hepatic function tests of the eight patients who died of hepatic failure in the shunt group were compared to those of 12 patients who died of variceal bleeding in the splenectomy group (Table 8). Except for the BSP retention ($p < 0.025$), there were no significant differences between the two groups in the preoperative hepatic function tests. A correlation has been found between the BSP retention and the logarithm of survival days from the day of BSP retention test to the day of death in ten patients who died of hepatic failure, eight in the shunt and two in the splenectomy group. Twenty points of these 10 patients are plotted on a scatter diagram (Fig. 1). The correlation

TABLE 4. *Types of Hepatic Disease*

	Splenectomy	Porta-systemic Shunt
Postnecrotic cirrhosis	12	21
Portal cirrhosis	13	15
Portal fibrosis	3	3
Schistosomiasis	2	2
Portal vein thrombosis & postnecrotic cirrhosis	0 (6)	1 (6)
Normal liver	1	0
	31	42

Chi-square = 0.9613, Probability > 0.1, d.f. = 2.

TABLE 5. *Survival of Patients with Portal Hypertension after Splenectomy (Life Table)*

Years after Surgery	Alive at Beginning of Interval	Died during Interval	Lost to Follow-up	Withdrawn Alive	Effective Number at Risk	Cumulative Survival Rate (%)	Standard Error of Cumulative Survival Rate (%)
0– 1	64	11	10	3	57.5	80.8	5.17
1– 2	40	2	2	0	39	76.7	5.63
2– 3	36	0	1*[1]	1	35	76.7	5.63
3– 4	34	1	2	1	32.5	74.3	5.89
4– 5	30	1	4*[2]	0	28	71.7	6.24
5– 6	25	0	1	3	23	71.7	6.24
6– 7	21	1	1	2	19.5	68.0	7.08
7– 8	17	0	0	2	16	68.0	7.08
8– 9	15	1	1	0	14.5	63.3	7.85
9–10	13	1	2	1	11.5	57.8	8.88
10–11	9	0	1	1	8	57.8	8.88
11–12	7	1	1	3	5	46.2	12.54
12–13	2	0	0	0	2	46.2	12.54
13–14	2	0	0	1	1.5	46.2	12.54
14–15	1	0	0	1	0.5	46.2	12.54

* [1]This patient and two patients in *[2] underwent mesocaval shunt because of repeated esophageal variceal bleeding 2 and 4 years after splenectomy, respectively.

TABLE 6. *Survival of Patients with Portal Hypertension after Porta-systemic Shunt (Life Table)*

Years after Surgery	Alive at Beginning of Interval	Died during Interval	Lost to Follow-up	Withdrawn Alive	Effective Number at Risk	Cumulative Survival Rate (%)	Standard Error of Cumulative Survival Rate (%)
0– 1	49	8	10	3	42.5	81.1	6.07
1– 2	28	0	1	3	26	81.1	6.07
2– 3	24	0	1*[1]	4	21.5	81.1	6.07
3– 4	19	3	0	2*[2]	18	67.6	8.60
4– 5	14	1	0	1	13.5	62.6	9.30
5– 6	12	1	0	5	9.5	56.0	10.39
6– 7	6	1	1	0	5.5	45.8	12.54
7– 8	4	0	0	0	4	45.8	12.54
8– 9	4	0	0	2*[3]	3	45.8	12.54
9–10	2	0	0	2	1	45.8	12.54

* [1]The patient was primarily operated upon with porta-caval shunt and was found to have thrombosed anastomosis postoperatively and had another shunt (meso-caval) at that time because of recurrent variceal hemorrhage.

* [2]One patient had an episode of variceal bleeding and received esophageal varices ligation one and a half years after mesocaval shunt.

* [3]One patient needed colon exclusion operation 4 years after porta-caval shunt.

TABLE 7. *Cause of Deaths*

Cause	Splenectomy	Porta-systemic Shunt	Chi-square	Probability
Hepatic failure	2	8	6.2330*[1]	$p < 0.025$ (d.f. = 1)
Variceal hemorrhage	12	3	4.0971*[2]	$p < 0.05$ (d.f. = 1)
Jaundice	1	1		
Hepatoma	1	1		
Cerebrovascular accident	1	0		
Shock due to postoperative non-variceal hemorrhage	1	1		
Cause unknown	1	0		
	19	14		

The values of chi-square were computed with continuity correction using the following tables.

*1

	Hepatic Failure	Non-hepatic Failure	Total
Splenectomy	2	17	19
Porta-systemic shunt	8	6	14

*2

	Variceal Hemorrhage	Not Bleeding	Total
Splenectomy	12	7	19
Porta-systemic shunt	3	11	14

TABLE 8. *Preoperative Liver Function of Patients Who Later Died of Variceal Hemorrhage in the Splenectomy and Hepatic Failure in the Porta-systemic Shunt Group*

	Splenectomy		Portasystemic Shunt	
	Mean	SE	Mean	SE
Albumin (Gm./dl)	4.06	0.02	3.54	0.01
Globulin (Gm./dl)	3.35	0.02	2.71	0.02
Zinc turbidity (unit)	14.36	3.40	12.55	1.66
Thymol turbidity (unit)	5 66	0.82	5.50	1.17
Mucoprotein (mg./dl)	67.50	32.4	67.00	13.49
Prothrombin time (sec.)	17.62	1.43	18.16	0.98
Bilirubin, total (mg./dl)	1.40	0.65	1.26	0.02
Cholesterol, total (mg./dl)	145.7	7.8	139.2	22.2
Cholesterol, ester (mg./dl)	80.5	0.5	74.3	26.8
Alkaline phosphatase (unit)	6.16	1.43	5.16	0.81
Bromsulphalein retention (45 min., %)	11.18	2.87	23.97	4.51
		(t-test, $p < 0.025$)		

coefficient is computed as -0.7092 ($p < 0.001$). By the method of least squares a straight line is fitted. When the BSP retention lies between 15 and 40, the regression equation is obtained as follows,

$$\log Y = 3.8325 - 0.0479\ X \pm 0.4036$$

where X: per cent of BSP retention (45 min.), Y: survival days and 0.4036 is the standard error of log Y.

As shown in Figure 1, the BSP retention obtained from the patients who died of hemorrhage has fallen lowerward in the straight line. This means that the regression line has reached a dead end in the natural history of hepatic cirrhosis with BSP retention at that level. Those patients who died of variceal bleeding did not reach the terminal of natural history and died untimely.

Discussion

Measurement of patient survival rate is necessary for evaluating the treatment of usually fatal chronic diseases.[8] However, concerning the effectiveness of preventing variceal hemorrhage, this does not seem to be completely true for instances of hepatic cirrhosis with portal hypertension. The present study showed that the cumulative survival rates in the splenectomy and the shunt groups were not significantly different by statistical test. Except that Edmunds[10] reported a higher survival rate in the shunt group than that of the non-surgical group,

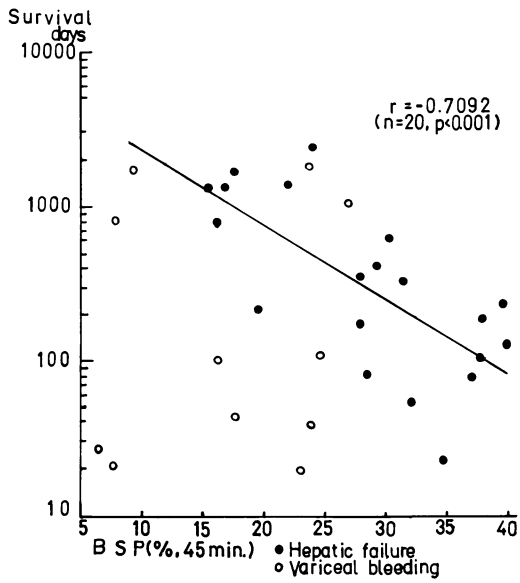

FIG. 1. Graph showing the correlation between the BSP retention and the survival days in those who died of hepatic failure. Those who died of variceal hemorrhage were also scattered for comparison. The regression equation fitted by the method of least squares is $\log Y = 3.8325 - 0.0479\ X \pm 0.4036$.

many other authors [5, 7, 12, 22] agreed that no difference existed between those with portasystemic shunts and the non-surgical group in survival rates. Although reports [14, 18, 20, 26] of the effectiveness of splenectomy in controlling bleeding varices in selected instances are available, the report of Hallenbeck [12] as well as this study showed that the survival rates were insignificantly different between the shunt and the splenectomy groups.

As for survival rates, no significant difference was found between those who underwent splenectomy and the shunt group, yet there were marked differences in the cause of deaths between the two groups. It has been found that the main cause of death in the splenectomy group was recurrent esophageal variceal hemorrhage and in the shunt group the main cause was hepatic failure. It seemed that the greatest influence of either splenectomy or portasystemic shunt was well reflected in the cause of death. The above mentioned authors [5, 7, 12, 22] also recognized that shunt would definitely protect esophageal varices from bleeding but did not improve the natural history of hepatic cirrhosis. Portasystemic shunt is more effective for control of bleeding esophageal varices than splenectomy, but the occurrence of hepatic faliure in the shunt group should be avoided by selection of patients.

The question now arises, is there any method to predict occurrence of hepatic failure after shunt procedure? Siegel [25] proposed a computer based index for prediction of operative survival in patients with cirrhosis and portal hypertension. This survival index has enabled preoperative separation of cirrhotic patients into three groups with markedly different probability of operative survival in whom there were no significant differences on the basis of hepatic function tests. But Siegel did not take portal hemodynamics into consideration of the survival index. Warren [27] has classified patients with portal hypertension into three groups and stressed the importance of hemodynamic studies. Smith [26] as well as Warren [28] have pointed out that those with cirrhosis and portal hypertension who have good portal flow are not indicated for portasystemic shunt. They found that hepatic failure appeared to be related to an abrupt reduction in portal flow caused by the acute diversion of flow through the shunt. To avoid postshunt hepatic failure, patients in whom portal flow is normal or mildly reduced should be considered candidates for splenectomy [26] or ablative surgical treatment.[17] However, Price [21] reported that no clear cut correlation could be established between overall results of operation and either preshunt or postshunt flow or per cent reduction in total hepatic flow in follow-up studies. Herman [15] also stated there was no correlation of pressure with prognosis of the patients. Attempts to assess the patients' condition prior to operation in terms of hepatic blood flow have not provided the answer.[2, 19]

On the other hand, some of the hepatic function tests were found to be related to survival after portasystemic shunt. Blakemore [3] reported that 64 patients with cirrhosis, having BSP retention averaging 21.1% (30 min.), were operated upon with postoperative mortality of only 9.3%, but BSP retention averaging 33.9% (30 min.) showed 39.9% mortality. Barker [1] also stated that prothrombin time, serum albumin, bilirubin and BSP retention seemed to have some prognostic significance. Hara [13] reported that operative mortality in patients with Child's classification of group A, B and C were zero, 9 and 53% respectively. Satterfield [22] reported that low white blood cell count, albumin and high bilirubin, prothrombin time, BSP retention and ascites influenced operative survival. In the nonsurgical series, Douglas [9] showed that increase in BSP retention indicated poor prognosis in hepatic cirrhosis. In Hirayama's

series [16] the cirrhotic patients with BSP retention over 25% (45 min.) showed the 3-year survival rate to be 30.3%, and Yoshitoshi [29] reported that eight of 11 patients with BSP retention over 30% (45 min.) died within 2 years. Although many authors agreed that impaired preoperative hepatic functions, e.g., low serum albumin, high bilirubin and increased BSP retention were related to increased mortality, the present study has revealed that only BSP retention is significantly different in the two groups.

The BSP retention was reported to be increased by shunt procedure in 46 per cent of patients in Ellis' series [11] and in 52 per cent of patients in Sedgwick's report.[24] Ellis stated that this test was not reliable as a guide to determine the wellbeing of the patients. Hallenbeck [12] reported that comparison of hepatic function tests performed before and at intervals of up to 42 months after portasystemic shunt offered no proof that hepatic function deteriorated with unusual rapidity during the first few years after portasystemic shunt. He also stated that some deterioration of hepatic function, rapid or slow, was characteristic of the natural history of cirrhosis of the liver, whether or not shunts were instituted.

The BSP retention is a function of four variables, namely hepatic uptake, storage, conjugation and biliary excretion.[4] If any one or more of these variables e.g. hepatic uptake is retarded by decrease in portal flow, the BSP retention may be increased. Therefore, it is assumed that if portal blood is diverted more completely by either intrahepatic shunt via capillarization of the sinusoids [23] or through the portasystemic shunt surgically constructed, it is more likely that BSP retention may increase. The present study has revealed that the occurrence of hepatic failure in the shunt group has definite relation to the significant increase in BSP retention. The nature of relationship between BSP retention and days of survival of those who later died of hepatic failure has been found to be most closely to approximate an exponential function. The regression equation proposed in this study is useful to predict days of survival of patients with cirrhosis and portal hypertension after shunt procedure. It can also indicate proper selection of patients for surgical treatment to reduce the incidence of hepatic failure. For example, if the BSP retention is 25% (45 min.), survival should be about 431 days. To avoid occurrence of hepatic failure, splenectomy and coronary vein ligation or ligation of esophageal varices may be preferable.

Summary and Conclusion

Of 109 patients with portal hypertension, 48 underwent portasystemic shunt and 61 were treated with splenectomy. The hospital death rates within 40 days of operation were 9.4% in the splenectomy group and 10.02% in the shunt group. The cumulative survival rates between the splenectomy and the shunt group did not show significant differences. Twelve of 19 deaths in the splenectomy group were due to variceal bleeding as contrasted to three of 14 deaths in the shunt group. Eight of 14 deaths in the shunt group were caused by hepatic failure, but only two out of 19 deaths in the splenectomy group were due to hepatic failure. It is apparent that portasystemic shunt largely protects cirrhotic patients from variceal hemorrhage but fails to improve the survival rate because of deaths from hepatic failure. The BSP retention was found to be the only factor related to hepatic failure after portasystemic shunt. A linear correlation has been found between the BSP retention and logarithm of the days of survival of those patients who later died of hepatic failure after operation. The regression equation offers the basis to predict the length of survival in patients who undergo shunt operation for portal hypertension.

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