A Randomized Trial for the Study of the Elective Surgical Treatment of Portal Hypertension in Mansonic Schistosomiasis

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From 1977 to 1983, 94 patients with esophageal varices and gastrointestinal bleeding secondary to mansonic schistosomiasis were entered into a prospective randomized trial comparing the three operations mainly used in Brazil: esophagogastric devascularization associated with splenectomy (EGDS, 32 patients), classical splenorenal shunt (SRS, 32 patients), and distal splenorenal shunt (DSRS, 30 patients). The randomization was interrupted because of a significant incidence of portosystemic encephalopathy (PSE) in the SRS group (26%), as compared to the DSRS (7%) and EGDS (0%) groups. The rate of rebleeding was the same in the three groups, but the rate of failure, as defined by the presence of technical problems, postoperative complications, or death, was significantly higher in the SRS group. This 2-year follow-up shows that SRS should be abandoned in hepatosplenic schistosomiasis and that a comparison between DSRS and EGDS with a longer follow-up is urgently needed.

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IN BRAZIL, the hepatosplenic form of mansonic schistosomiasis is responsible for a large number of bleeding esophageal varices. This complication is by far the most frequent cause of death in schistosomiasis.[1] For the surgical treatment of this condition, direct portocaval shunt is no longer used because it has been demonstrated that its causes portosystemic encephalopathy (PSE) in more than 50% of the cases.[2,3] On the other hand, spontaneous PSE is rarely, if ever, observed in nonoperated patients with hepatosplenic schistosomiasis.[4] Furthermore, the natural history of the disease shows that patients without bleeding episodes may have a long-term survival, frequently more than 20 years.[5]

Mansonic schistosomiasis is therefore a good human model for the study of portal hypertension in the virtual absence of parenchymal liver injury. Thus, any postoperative change in the hepatic function basically could be attributed to the operation itself rather than to the underlying liver disease.

Three operations are mainly used in our country for the treatment of portal hypertension due to schistosomiasis[6]: esopagogastric devascularization associated with splenectomy (EGDS), classical splenorenal shunt (SRS), and distal splenorenal shunt (DSRS). No prospective studies comparing these operations have so far been performed in schistosomiasis.[7]

A few years ago Hassab, in Egypt, reported very good retrospective results for the treatment of bleeding varicose veins employing esophagogastric devascularization. However, his cases included patients with schistosomiasis as well as other liver diseases. Furthermore, the surgical indications were for emergency, elective, and prophylactic purposes.[8-10]

Our investigations started in 1977 to compare the above-mentioned operations in adult patients and involved the following variables: (a) operative and late mortality; (b) rebleeding varices; and (c) portosystemic encephalopathy. This paper will present the results of a 2-year follow-up study.

Patients and Methods

Patients Studied

Patients with hepatosplenic schistosomiasis, a history of gastrointestinal bleeding, and esophageal varices demonstrated by endoscopy were considered for inclusion in

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this study according to the following criteria: (1) 18 to 55 years of age; (2) minimum interval between last hemorrhage and operation, 15 days; (3) chemotherapy of schistosomiasis before operation; (4) absent or easily controllable ascites; and (5) absence of liver failure, cirrhosis, chronic alcoholism, diabetes, heart and renal failure, peptic ulcer, and angiographic evidence of portal thrombosis.

The diagnosis of schistosomiasis was based on epidemiological, clinical, and parasitological findings and subsequently was confirmed at surgery, when a liver biopsy was performed.

Only patients who agreed to be operated on were included in this investigation. For the following ethical reasons, a control, nonoperated group was not considered[6]: (1) bleeding from esophageal varices is by far the most frequent cause of death in schistosomiasis[1]; (2) mortality in nonoperated patients who rebleed or in those operated on during a bleeding episode varies from 20 to 30%[5,11]; (3) patients frequently migrate to areas in the country where medical care is poor; and (4) it has been demonstrated that patients whose rebleeding was prevented by surgical treatment can survive for more than 20 years.[5]

Laboratory tests that were routinely performed before and after operation were: (a) in the blood-total, direct- and indirect-reacting bilirubin, aminotransferase (AST and ALT), gama-glutamyltransferase, alkaline phosphatase, prothrombin time, serum protein electrophoresis, urea, and the surface antigen of the B viral hepatitis (HBsAg); (b) routine urine examination; and (c) parasitological examination of the stools by the method of Kato–Katz[12] for the counting of schistosomal eggs.

Patients considered for inclusion were submitted to superior mesenteric and celiac arteriograms and/or splenoportography in order to study the patency of portal and splenic veins.

Randomization in three groups, according to a table of random numbers, was applied to 94 patients.[13] Each type of operation was always performed by the same surgical team, which had a wide experience in this field. Randomization was interrupted because of the significant number of patients with encephalopathy after splenorenal shunt. One patient allocated to the SRS group died during the induction of anesthesia and was dropped from the study.

Types of Surgery

One of three operations was performed[6]: (1) esophagogastric devascularization associated with splenectomy (EGDS); (2) classical splenorenal shunt (SRS); (3) distal splenorenal shunt (DSRS).

Technical Aspects

In all three operations, the abdominal cavity is opened by a large left paramedian incision. Care must be taken to achieve a good hemostasis, and the abdominal cavity is never drained.

Esophagogastric devascularization associated with splenectomy (EGDS). This is a relatively simple procedure, widely used in our country. The first surgical step is a lost ligature of the splenic artery near the body of the pancreas. Then, the splenectomy is done. The proximal stomach is devascularized from the incisura angularis up to the esophagus. The frenoesophageal membrane and vagal trunks are sectioned to allow for the mobilization of the terminal esophagus. The terminal esophagus (7–8 cm) and proximal stomach are sectioned with a longitudinal incision sectioning all layers on the anterior face. Each varicose trunk is sutured with chrome catgut and running stitches starting at the stomach and ending as high as possible in the esophagus. Esophagus and stomach are closed in two planes with monofilament thread. The first plane involves all the layers, with knots placed in the lumen. The second plane is done with a running suture involving the esophageal layer and stomach seromuscular one. The next step is a 270 degree antireflux valve, in which the stomach fundus is anteriorly sutured to cover the esophagus and stomach incisions. The operation is completed by a pyloroplasty. The patient is maintained with a nasogastric tube for 7 days, and total parenteral nutrition is given during this period.

Classical splenorenal shunt (SRS). Through the inframesocolic approach, the inferior mesenteric vein is dissected to permit access to the splenic vein behind the body of the pancreas. The pancreatic branches of the splenic veins are ligated, and the splenic vein is dissected for about 5–7 cm towards the splenic hilum. The left renal vein is undermined from the retroperitoneum for about 4 or 5 cm. The adrenal and gonadal veins are ligated. After clamping, the splenic vein is sectioned close to the tail of the pancreas. The left renal vein is clamped with a Satinsky clamp, and a linear section is done on the cranial face of the renal vein. The anastomosis is done with a running suture on the posterior wall and with an interrupted one on the anterior wall. The patient is fed after normal bowel movements usually on the second or third postoperative day.

Distal splenorenal shunt (DSRS). The first step is the opening of the gastrocolic epiploon so as to reach the epiploon retrocavity. The splenic artery is temporarily clamped close to the body of the pancreas. Next, the inferior border of the pancreas is carefully dissected to provide access to the splenic vein, which is dissected up to the portal vein for about 8 cm. The portal vein behind the pancreas is dissected to supply an adequate length for placing a spoon vascular clamp and ligating the left gastric vein at its origin. The right gastroepiploic vein is ligated at its origin in the superior mesenteric vein. The left renal vein is dissected in the retroperitoneum, beginning at the

renal hilum. Both the gonadal and adrenal veins are ligated.

A running suture is done involving the retroperitoneal tissue located along the splenic, superior mesenteric, and renal veins. This suture is placed to ligate all lymphatic vessels sectioned during the renal vein dissection. A bed is formed on which the shunted splenic vein will be placed. After the portal and splenic veins are clamped adequately, the splenic vein is sectioned close to the portal vein. The opening on the portal side is closed with a running 5-0 thread suture to create a perfect anatomic continuity between the superior mesenteric and portal veins. The splenic and renal vein anastomosis should be done at a 45 degree angle on the upper face of the renal vein. This situation usually corresponds to the adrenal vein that was ligated. The anastomosis is performed with a running suture on the posterior wall and an interrupted one on the anterior wall. The right gastric vein is ligated close to the duodenum and the umbilical vein close to the umbilical ligament. The patient is fed after normal bowel movements.

Criteria of Evaluation

To establish whether the three groups were comparable, the following variables were statistically analyzed: sex, age, presence and degree of bleeding, size of the liver and of the spleen, serum total (TB) and indirect-reacting bilirrubinemia (IB), aspartate (AST) and alanine aminotransferase (ALT), prothrombin time (PT) and serum albumin (SA).

Although some of the 94 patients have already completed the 5-year period of follow-up, those operated on in 1980 and 1981 have not yet completed their total follow-up time. In August 1983, the last patient admitted to the trial completed 2 years of follow-up, and therefore we decided to do the first statistical analysis including all the patients on their first 2 years of follow-up.

The main complications considered for analysis were encephalopathy and recurrence of gastrointestinal bleeding. We have also analyzed a third criterion, that of general success or failure of the treatment. Success was considered if the patient was alive and without complications after the follow-up time. Failure was considered when: (1) death had occurred from either the disease or the treatment; (2) technical problems had not permitted the performance of the surgery as originally proposed; (3) the patient had developed one of the two major complications after surgery, namely encephalopathy or upper gastrointestinal bleeding.

Portosystemic encephalopathy (PSE) characterized by steady or fluctuating neuropsychiatric symptoms was graduated as: (a) mild when easily controllable by the restriction of protein, with or without neomycin; (b) moderate when the neuropsychiatric symptoms were more severe, often recurrent but still clinically controllable; and (c) severe when PSE caused major disability and required hospitalization for control.

Statistical Analysis[14,15]

For the comparison of quantitative variables, univariate and multivariate (Wilks statistic) analyses of variance were used to compare the three groups. A logarithmic transformation was used for some biochemical variables (see Table 3) in order to obtain a better approximation to the normal distribution.

Qualitative variables such as sex, recurrence of bleeding encephalopathy, and success or failure of treatment were analyzed by standard frequency tables procedures (χ^2 tests).

All computations were performed with the SAS[15] (Statistical Analysis System) on an IBM/370-155 computer (Instituto de Pesquisas Energéticas e Nucleares, University of S. Paulo, Brazil).

Follow-up

Four patients were lost to follow-up during the period of 2 years, distributed in the three surgical groups (two for EGDS, one for PSRS, and one for DSRS). To treat the four censored data, we considered all the extreme possibilities that could have occurred to them and studied the consequences of these conceptual outcomes.

Four hypotheses were considered:

Hypothesis A. Each event (PSE, recurrence of bleeding, or general failure) was analyzed without considering the four cases lost to follow-up.

Hypothesis B. The same event was analyzed considering that none of the four cases have had the complication under study.

Hypothesis C. The event was analyzed considering that all the four patients have had the complication.

Hypothesis D. We have separated two groups, putting the absence of the complication exactly in the surgical group where its occurrence was most probable and considering the other lost patients of the two other surgical groups as having the complication.

Results

Preoperative Comparison of the Three Surgical Groups

Tables 1, 2, and 3 show the comparability of the three groups. They did not differ significantly with regard to age, sex, liver and spleen size, degree of bleeding and serum bilirubin, transaminases, albumin and prothrombin time.

Technical Problems

SRS group. In one patient, SRS could not be performed and an EGDS was carried out. This case was considered a failure.

TABLE 1. *Clinical Data in the Three Surgical Groups*

Group	No. of Patients	Age	Sex (No., %) F	Sex (No., %) M	Liver Size (cm)	Spleen Size (cm)
SRS	32	30.72 ± 8.88	9 (28.1)	23 (71.9)	4.97 ± 3.15	9.78 ± 5.03
SGED	32	30.03 ± 10.00	9 (28.1)	23 (71.9)	5.31 ± 2.97	9.41 ± 4.30
DSRS	30	34.13 ± 8.78	13 (43.3)	17 (56.7)	6.07 ± 3.43	10.20 ± 5.47
		p = 0.1829	p = 0.3435		p = 0.3875	p = 0.8197

EGDS group. EGDS and splenectomy could be performed in all randomized patients of this group.

DSRS group. DSRS could be performed in all patients. One patient rebled 17 months after the operation and was submitted to EGDS. Preoperative angiography had shown a thrombosis of the shunt.

Portosystemic Encephalopathy (PSE)

SRS, EGDS, and DSRS groups showed the following incidence of PSE: 8/31 (25.8%), 0/30, and 2/29 (6.9%), respectively. As one, two, and one patients were lost to follow-up, the above-mentioned hypotheses A, B, C, and D were considered. For hypothesis A, B, and C, a significant difference among the three groups was observed (Table 4). For hypothesis D, a p = 0.0720 was observed.

Encephalopathy became rapidly severe in four out of eight patients of the SRS group. On the other hand, EPS was slight and moderate in the two patients of the DSRS group.

Recurrent Gastrointestinal Hemorrhage (RGIH)

SRS, EGDS, and DSRS groups showed the following incidence of RGIH: 4/31 (12.9%), 4/30 (13.3%), and 2/29 (6.9%), respectively. Considering the same four hypotheses, no significant difference was found among the three groups (Table 4).

Failure

Failure, as previously defined, was observed in 15/31 (48.4%), 4/30 (13.3%), and 5/29 (17.2%) patients from the groups SRS, EGDS, and DSRS, respectively. Considering the same four hypotheses, a significant difference was observed among the three groups. Statistical analysis showed that the SRS group differed significantly from the other groups (Table 4).

Mortality

Only two deaths were observed in the studied patients, and both belonged to the SRS group.

Discussion

This randomized trial showed two main results: (1) the classical (proximal) SRS imposes a high risk of encephalopathy.[16] This complication was significantly less frequent after the selective shunt (DSDR) and was not seen after splenectomy with esophagogastric devascularization (EGDS); and (2) rebleeding can be observed with equal frequency after the three types of operation when a follow-up period of 2 years is considered.

The significantly greater incidence of encephalopathy was not statistically detected in the SRS group in one hypothesis only, the SRS patient lost to follow-up being considered as not having the complication and all three patients of the other two groups (two from the EGDS and one from the DSRS group) being considered as having encephalopathy. This possibility, however, is extremely unlikely, as encephalopathy is rarely, if ever, seen after EGDS.[3,5]

In liver cirrhosis, the incidence of PSE after portal decompression and after DSDR has been similar according to some authors[17-19] and significantly different according to others.[16,20-24] It must be emphasized, however, that interposition graft for portal decompression was used in a large number of patients in some trials.[17,21] It is well known that such grafts tend to thrombose,[6,24] and therefore the decompressive effect may be jeopardized. It is also possible that such discrepant results may be due to different etiologies of cirrhosis, especially concerning alcoholism.

Zeppa, Hutson, Levi, and Livingstone[25] emphasize that such operations should be compared in nonalcoholic patients where DSRS produces less encephalopathy than portal decompression, whereas in alcoholics such differences may not be detected. Whatever the cause, however, it is hard to evaluate the importance of hepatocellular failure and of progressive liver injury in each case.

Hepatosplenic schistosomiasis is characterized by marked circulatory changes and consequent portal hy-

TABLE 2. *Degree of Preoperative Bleeding in the Three Surgical Groups*

Group	Slight	Moderate	Severe	Total
SRS	4 (12.5%)	11 (34.4%)	17 (53.1%)	32 (100.0%)
SGED	2 (6.3%)	13 (40.6%)	17 (53.1%)	32 (100.0%)
DSRS	5 (16.7%)	10 (33.3%)	15 (50.0%)	30 (100.0%)

$\chi^2 = 1.77$.
p = 0.7777.

TABLE 3. *Biochemical Data in the Three Surgical Groups*

Variables	Groups	No. of Patients	Average ± SD	Limits Max.	Limits Min.
TB (mg %)*	PSRS	32	0.92 ± 0.41	0.25	1.53
	SGED	32	0.86 ± 0.33	0.50	1.70
	DSRS	28	0.97 ± 0.63	0.21	2.63
IB (mg %)*	PSRS	32	0.37 ± 0.26	0.08	1.10
	SGED	32	0.28 ± 0.19	0.02	1.00
	DSRS	28	0.32 ± 0.19	0.00	0.80
AST (IU/L)*	PSRS	32	35.31 ± 38.25	3.00	186.00
	SGED	32	44.56 ± 36.58	8.00	182.00
	DSRS	28	38.93 ± 27.72	9.00	108.00
ALT (IU/L)*	PSRS	32	30.72 ± 25.77	5.00	145.00
	SGED	32	37.00 ± 29.99	7.00	122.00
	DSRS	28	36.11 ± 27.40	4.00	107.00
PT (%)†	PSRS	32	73.84 ± 13.52	38.00	100.00
	SGED	32	74.09 ± 16.70	33.00	100.00
	DSRS	30	78.33 ± 19.39	33.00	100.00
SA (mg %)‡	PSRS	32	3.76 ± 0.59	2.32	4.52
	SGED	32	3.73 ± 0.49	2.96	5.12
	DSRS	30	3.67 ± 0.61	2.30	4.80

* $F_{(8.172)} = 0.98$; $p = 0.4548$ (after logarithmic transformation).
† $F_{(2.91)} = 0.70$; $p = 0.4974$.
‡ $F_{(2.91)} = 0.22$; $p = 0.8048$.
For abbreviations, see Methods.

pertension in the absence of significant alterations in liver function. Thus, it offers an opportunity to discriminate the effects of each operation.[26] Furthermore, an important characteristic of schistosomotic fibrosis is its tendency to be nonprogressive in some patients submitted to antischistosomal chemotherapy and living in nonendemic areas. This might explain the significant number of patients followed up for more than 20 years in a nonendemic area such as São Paulo City and without signs of progressive liver disease (unpublished data). The same results were obtained in a long-term follow-up study in patients submitted to EGDS in an endemic area.[5] The uniformity of the schistosomotic process minimizes the large number of variables inherent in the cirrhotic population,[26] and for that matter postoperative changes can be confidently attributed to circulatory and hemodynamic alterations yielded by the surgical procedure.

In contrast with blood ammonia levels in cirrhotic patients, those in schistosomotic patients after a hematemesis are either normal or only slightly raised. After a portacaval shunt, however, liver function tests and ammonia tolerance become abnormal, and a large proportion of these

TABLE 4. *Chi-Square Values for A, B, C, and D Hypotheses (See Text)*

Hypothesis	Encephalopathy* Chi-Square	Encephalopathy* p	Digestive Bleeding Chi-Square	Digestive Bleeding p	Success or Failure Chi-Square	Success or Failure p
A	$\chi^2 = 11.05$*	0.0040	$\chi^2 = 0.7724$	0.6796	$\chi^2 = 11.52$	0.0031
	$\chi_1^2 = 10.34$	0.0057	—	—	$\chi_1^2 = 11.45$	0.0033
	$\chi_2^2 = 0.71$	0.7009	—	—	$\chi_1^2 = 0.12$	0.9443
B	$\chi^2 = 11.25$	0.0036	$\chi^2 = 0.7311$	0.6938	$\chi^2 = 11.77$	0.0028
	$\chi_1^2 = 10.52$	0.0052	—	—	$\chi_1^2 = 11.63$	0.0030
	$\chi_2^2 = 0.73$	0.6961	—	—	$\chi_2^2 = 0.14$	0.9307
C	$\chi^2 = 6.87$	0.0322	$\chi^2 = 0.96$	0.6201	$\chi^2 = 9.49$	0.0087
	$\chi_1^2 = 6.70$	0.0350	—	—	$\chi_1^2 = 9.48$	0.0087
	$\chi_2^2 = 0.17$	0.9177			$\chi_2^2 = 0.01$	0.9942
D	$\chi^2 = 5.26$	0.0720	$\chi^2 = 2.03$	0.3627	$\chi^2 = 7.82$	0.0200
	—	—	—	—	$\chi_1^2 = 7.80$	0.0202
	—	—	—	—	$\chi_2^2 = 0.01$	0.9946

* χ^2 tests the hypothesis of homogeneity among the three groups.
χ_1^2 tests the hypothesis that groups EGDS and DSRS differ from group SRS.
χ_2^2 tests the hypothesis of equality between groups EGDS and DSRS.

individuals develop chronic PSE.[27] Thus, in schistosomiasis, PSE would be due to the surgical shunts and not to natural collateral circulation or to the malfunctioning injured hepatic parenchyma.

The present trial shows that portal decompression through splenorenal shunt produces PSE in a large number of cases and that after DSRS encephalopathy is significantly less frequent. Since right-to-side collateral circulation is observed by angiography soon after DSRS,[7] we may speculate that this circulation would be less prone to produce PSE in schistosomiasis.

In conclusion, our data show not only that DSRS is superior but that SRS should be abandoned in hepatosplenic schistosomiasis. On the other hand, a comparison between DSRS and EGDS with more patients and a longer follow-up is urgently needed.

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