

Liver Transplantation during Fifty-Three Years' Experience with Randomized Controlled Trials of Emergency Portacaval Shunt for Bleeding Esophageal Varices in Cirrhosis

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Abstract

Background: Currently, emergency treatment of Bleeding Esophageal Varices (BEV) consists mainly of endoscopic and pharmacologic measures, with use of TIPS when bleeding is not controlled. Surgical shunt has been relegated to salvage of survivors of failed endoscopic, pharmacologic, and TIPS treatment. We have conducted 10 prospective studies of Emergency Porta Caval Shunt (EPCS) during 46 years.

BEV in cirrhosis has been considered an indication for Liver Transplantation (LT) by some respected LT programs. This important issue was examined in our two recent Randomized Controlled Trials (RCTs) in 365 unselected, consecutive patients with acute BEV conducted from 1988 to 2011.

Study design: In RCT No. 1, 211 unselected, consecutive cirrhotic patients with acute BEV ("all comers") were randomized to Emergency Endoscopic Sclerotherapy (EEST) (n=106) or EPCS (n=105). In RCT No. 2, 154 unselected consecutive cirrhotic patients with acute BEV ("all comers") were randomized to TIPS (n=78) or EPCS (n=76). In each RCT, the two treatment groups were compared with regard to effect on survival, control of bleeding, encephalopathy, and direct cost of care. Diagnostic workup was completed within 6 hr and primary treatment was initiated within 8 to 12 hours. Regular follow-up was accomplished in 100% of patients. In RCT No. 1, 96% of patients underwent more than 10 years of follow-up, or until death. In RCT No. 2, follow-up lasted for 5 to 10 years in 85%, and 3 to 4.5 years in the remainder. Patients were evaluated for LT on admission and at regular intervals thereafter. In addition to the two RCTs, the analysis of LT was supplemented in 1300 unrandomized cirrhotic patients who previously underwent Porta Caval Shunt (PCS) with 100% follow-up.

Results: Clinical characteristics of each group were similar at the time of enrollment. The distribution of patients in Child risk classes was almost identical in the two groups in each RCT. Almost one-third of patients in each group were in Child class C. Permanent control of bleeding was achieved by sclerotherapy in only 20% and by TIPS in only 22%. In contrast, EPCS permanently controlled bleeding in 97% to 100% ($p<0.001$). Sclerotherapy and TIPS patients required twice as many units of blood transfusion as EPCS patients. Survival rate at all time intervals and in all Child classes was significantly greater following EPCS than after sclerotherapy and TIPS ($p<0.001$). Median survival was over 10 years following EPCS, compared to 1.99 years following TIPS. EPCS remained permanently patent in 97% of patients. In contrast, stenosis or occlusion of TIPS was demonstrated in 84% of patients, 63% of whom underwent TIPS revision, which failed in 80%. Recurrent episodes of encephalopathy developed in 35% of sclerotherapy patients and 61% of TIPS patients. In contrast, encephalopathy occurred in 15% of EPCS patients in RCT No. 1 and 21% of EPCS patients in RCT No. 2. Direct costs of care, measured as charges per year, were 5 to 7 times greater in the sclerotherapy group (\$168,100) and TIPS groups (\$264,800) than in the EPCS group (\$39,000) ($p<0.001$).

Of the 365 randomized patients in the two RCTs, only 23 (6.3%) were ultimately referred for LT, mainly because of progressive liver failure. Of these, only 11 (3%) were approved for LT, and only 8 (2.2%) underwent LT. One- and 5-year LT survival rates were 0.68% and 0, compared to 81% and 73% after EPCS. In the 1300 unrandomized PCS patients, 50 (3.8%) were referred and 19 (1.5%) underwent LT. Five-year survival rate was 53% compared to 72% for all 1300 patients.

Conclusions: EPCS was uniformly effective in treatment of BEV, while sclerotherapy and TIPS were disappointing. EPCS permanently stopped variceal bleeding, almost never became occluded, accomplished long-term survival that was more than 5 times survival rate following sclerotherapy or TIPS, and was much less costly than sclerotherapy or TIPS. If bleeding is permanently controlled, as occurred invariably following EPCS, cirrhotic patients with BEV seldom require LT. PCS is effective first-line and long-term treatment. Should LT be required in patients with PCS, although technically more demanding, numerous studies have shown that PCS does not increase mortality or complications. Neither EST nor TIPS are effective emergency or long-term therapeutic measures.

Abbreviations: LT: Liver Transplantation; BEV: Bleeding Esophageal Varices; TIPS: Transjugular Intrahepatic Portosystemic Shunt; EPCS: Emergency Portacaval Shunt; PSE: Portal Systemic Encephalopathy; RCT: Randomized Controlled Trial; UCSD: University of California, San Diego; UGI: Upper Gastrointestinal; ICU: Intensive Care Unit; PCS: Portacaval Shunt; EGD: Esophagogastroduodenoscopy; EEST: Emergency Endoscopic Sclerotherapy; HV: Hepatic Vein; IVC: Portal Vein; PV: Portal Vein; PRBC: Packed Red Blood Cells; PTFE: Polytetrafluorethylene; HGPCS: Prosthetic H-Graft Portacaval Shunt; DSRS: Distal Splenorenal Shunt

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Introduction

Bleeding Esophageal Varices (BEV) is a common and highly lethal complication of cirrhosis. Numerous studies have shown that BEV is responsible for much of the high mortality rate associated with cirrhosis [1,2]. If the varices remain untreated after recovery from a bout of acute bleeding, we [3] and others [4] observed a 95% incidence of recurrent bleeding, and death within 2 to 5 years in 90% to 100% of the patients.

A number of modalities are used today for treatment of acute BEV, including endoscopic variceal ligation, endoscopic sclerotherapy, pharmacologic measures and, if these fail to obtain immediate and prolonged control of bleeding, Transjugular Intrahepatic Portosystemic Shunt (TIPS). Surgical Portal-Systemic Shunt (PSS) is infrequently used today, in large part because of the belief, unsubstantiated by prospective randomized controlled trials involving unselected patients, that surgical shunts cause frequent Portal-Systemic Encephalopathy (PSE) and liver failure. Consequently, surgical PSS has been relegated to the seldom used salvage of survivors of failed endoscopic, pharmacologic, and TIPS treatment.

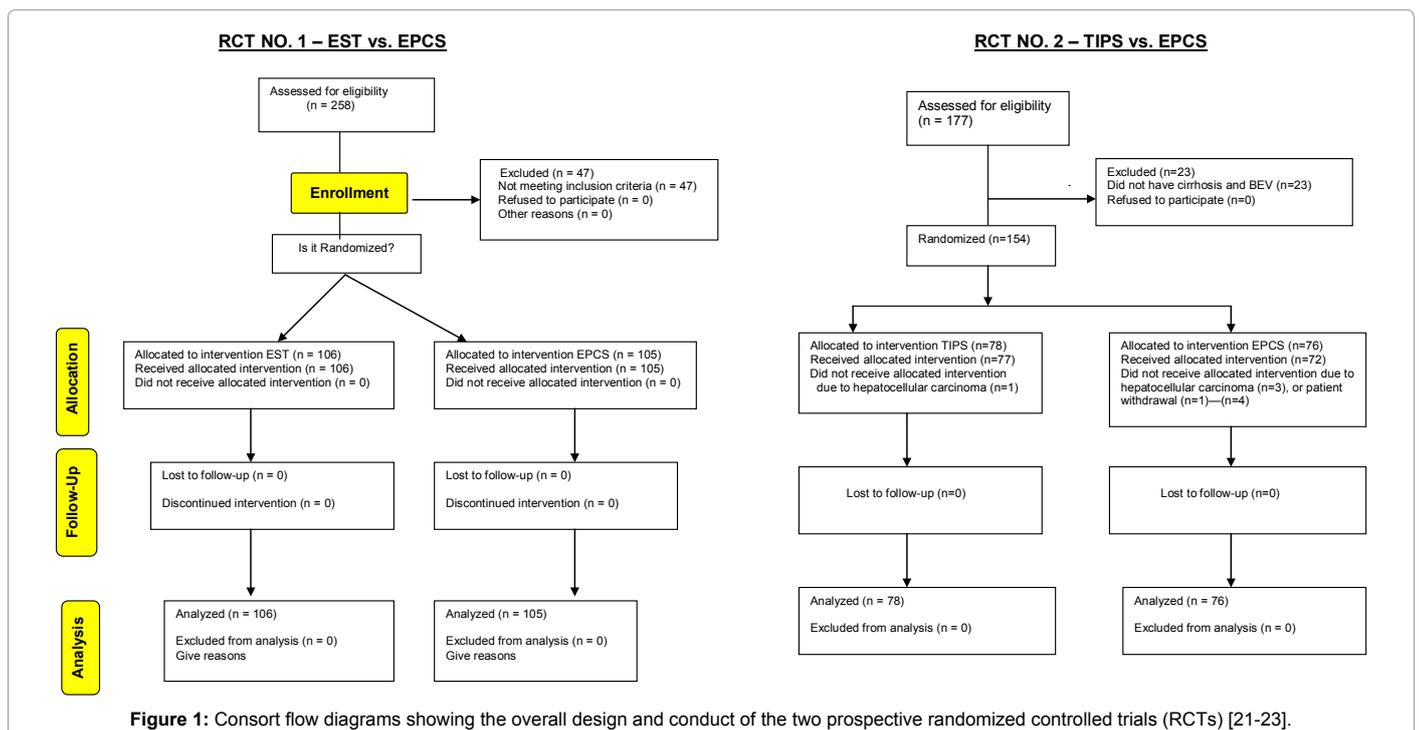
Liver Transplant (LT) is the only curative treatment of cirrhosis. Some respected transplant centers have considered BEV in cirrhosis to be an indication for LT. It has been proposed that LT be considered the treatment of choice for "patients with advanced liver disease after failure of sclerotherapy" [5,6] and for "all patients with end-stage liver disease (group C) and variceal bleeding... in the absence of any contraindications" [5-7]. Regrettably, there have been no randomized controlled trials of LT following any of the emergency modalities of therapy for BEV to support or contradict these proposals. All reported data on LT in patients with BEV have been based on retrospective reviews of medical records. Furthermore, recommendations regarding LT in patients with BEV generally have not taken into account the well known limitations, particularly insufficient donor organs.

During the 53 years from 1958 to 2011 we performed 10 prospective studies of EPCS [8-17]. A total of 956 patients were involved in these

studies of acute BEV, which is the largest reported experience with EPCS in the world. The unique features of our studies that, together, make them different from other reported investigations are as follows: (1) EPCS was undertaken within 20 hrs of initial contact of the patient with our institution, usually within 8 hrs; (2) the patients were unselected and consecutive, which means that all patients with bleeding varices ("all comers") regardless of their condition, were entered in the studies and treated; (3) the studies were prospective, which means that the patients were managed according to a well-defined and consistently applied protocol, and specific data were collected at the time of diagnosis, treatment, and follow-up; and (4) the patients were followed up monthly for the first year and every 3 months thereafter for life, such that the 1-, 5-, and 10-years follow-up rates were 100, 98, and 97%, respectively.

Our most recent studies of EPCS have been two consecutive Randomized Controlled Trials (RCTs) in unselected, consecutive patients with acute BEV. The first of these RCTs (RCT No. 1) compared Emergency Endoscopic Sclero Therapy (EEST) versus EPCS in 211 unselected consecutive patients from April 8, 1988, until December 31, 2005. It was known as the San Diego Bleeding Esophageal Varices Study [15,16]. The second RCT (RCT No. 2) compared TIPS versus EPCS in 154 unselected consecutive patients with acute BEV [17]. It was undertaken after entry in the first RCT had ended and was separate and distinct from the first RCT. It was conducted from July 25, 1996, until July 31, 2011. These two RCTs will be discussed in detail in this report.

In both of our RCTs, beginning with the index admission and regularly thereafter, all patients were evaluated by the UCSD liver transplantation program for indications for LT. If and when patients exhibited progressive liver failure, they underwent extensive evaluation for LT. As part of our analysis, we examined the question of the need for LT after the life-threatening problem of BEV had been addressed [18]. In addition, the effect of EST or EPCS on the conduct and outcome of LT was examined.



As a supplement to the RCT data, we have analyzed our results regarding LT in 1300 unrandomized referred patients in whom we performed Porta Caval Shunt (PCS) beginning in 1978, 600 as an emergency PCS and 700 electively.

Patients and Methods

Design of RCTs No. 1 and No. 2

Figure 1 is a Consort Flow Diagram that shows the overall design and conduct of the two RCTs [19-21]. In unselected, consecutive patients ("all comers") who entered UCSD Medical Center with acute BEV, the objectives were to compare Emergency Direct Porta Caval Shunt (EPCS) versus EEST in RCT No. 1 and versus TIPS in RCT No. 2 with regard to influence on survival, control of bleeding, PSE, and economic costs. Ninety-one board-certified gastroenterologists, emergency physicians, and surgeons in the counties of San Diego, Imperial, Orange, and Riverside, with a population of 8.5 millions, agreed to promptly refer all of their patients with acute BEV to UCSD Medical Center for entry into the RCT. Patient entry in RCT No. 1 lasted from April 8, 1988, until July 25, 1996, and follow-up continued until December 31, 2005, 17 and $\frac{3}{4}$ years after the start of the study. Patient entry in RCT No. 2 lasted from July 25, 1996, until October 8, 2003, and follow-up continued until July 31, 2011, 15 years after the start of the study.

Our recent publications [15,17] described our RCTs and provided full information on the protocols and methods. These include (1) design of study; (2) patient eligibility; (3) definitions (bleeding esophageal varices (BEV), unselected consecutive patients ("all comers"), Emergency Endoscopic Sclerotherapy (EEST), long-term Endoscopic Sclera Therapy (EST), Emergency Porta Caval Shunt (EPCS), TIPS, failure of emergency primary therapy, failure of long-term therapy, rescue therapy, informed consent; (4) randomization; (5) diagnostic work-up; (6) quantitative Child's classification; (7) initial emergency therapy during work-up; (8) Emergency Endoscopic Sclero Therapy (EEST); (9) Emergency Portacaval Shunt (EPCS); (10) TIPS; (11) post-treatment therapy; (12) lifelong follow-up; (13) quantitation of Portal-Systemic Encephalopathy (PSE); (14) data collection; (15) direct costs of care; (16) TIPS-specific follow-up.

Eligibility

All patients without selection with Upper Gastrointestinal (UGI) bleeding, defined as blood in the esophagus, stomach or duodenum, who entered the UCSD emergency department directly, or were transferred to UCSD from an area hospital, or developed bleeding while hospitalized in UCSD Medical Center were eligible for investigation. Such patients were enrolled in the RCT if they met the following 5 conditions: (1) requirement for two or more units of blood transfusion, (2) clinical and laboratory findings of cirrhosis, (3) upper endoscopy that showed esophageal varices, (4) no other lesion that could reasonably account for bleeding of the observed magnitude, and (5) UGI bleeding that had been observed within 48 hr of study entry and, therefore, was considered acute bleeding.

Informed consent

Informed consent was obtained by a physician co-investigator, from every patient before randomization to the treatment groups, and was witnessed by a third party who was not involved in the study. Consent was obtained after the patient was given a thorough explanation of the study, including the risks and benefits of all treatment options, including those not involved in the RCT. The procedure for obtaining consent and the consent form were regularly reviewed and approved by

the Human Subjects Committee (Institutional Review Board) and the National Institutes of Health (NIH).

Randomization

After emergency endoscopy demonstrated esophageal varices and no other lesion that could reasonably account for the bleeding, the diagnostic workup provided clear evidence of cirrhosis of the liver, and informed consent was obtained, the patients were randomized by drawing a card from an opaque sealed envelope, to either an EEST group or an EPCS group in RCT No. 1, or to either TIPS or EPCS in RCT No. 2. Sealed designation cards were prepared by a statistician according to a computer-generated block randomization design, without the knowledge of the physicians participating in the study.

Direct cost of care

There have been no reports of the costs of any of the widely used forms of emergency treatment of BEV. In each RCT, the two groups were compared with regard to direct costs of care [16]. Complete UCSD charges were obtained for every patient entered in each RCT continuously for more than 10 years. In addition, all referring hospitals and referring physicians signed agreements to provide complete records of charges as they occurred. Prior to initiation of the study, UCSD Medical Center agreed to promptly provide copies of all hospital and outpatient charges on all patients at the time when the patients and insurance carriers were billed. Similarly, the UCSD Medical Group, which does the professional fee billing for all physicians who care for patients at UCSD Medical Center, agreed to promptly provide copies of all professional fee bills.

Unrandomized portacaval shunt patients

Beginning in 1978 when LT became available to us, we performed Porta Caval Shunt (PCS) for BEV in 1300 referred cirrhotic patients at UCSD Medical Center Hospitals and the San Diego Veterans Administration Hospital. Patients were studied prospectively according to a well-defined protocol with on-line data collection to determine the indications for subsequent LT. The diagnostic work-up was identical in the unrandomized patients and the RCT patients. From 1978 until the start of our RCT in 1988, EPCS was performed for acute variceal bleeding within 8 hours of initial contact in 600 unselected patients, all comers included. Elective PCS was done over a period of 20 years in 700 selected patients referred to us only after recovering from one or more bouts of BEV elsewhere. Follow-up rate was 100% at 5 years and 97% at 10 years.

Statistical analysis

The survival rates in the EST and EPCS groups in RCT No. 1 and in the TIPS and EPCS groups in RCT No. 2, and in the subgroups determined by the Child's risk class were calculated and plotted using the Kaplan-Meier method, and compared using the log-rank test. Statistical comparisons between the EST and EPCS groups in RCT No. 1 and between the TIPS and EPCS groups in RCT No. 2 were performed as follows: The proportion of subjects referred for LT evaluation, the proportion approved for LT, and the diagnosis of the LT candidates, were compared using Fisher's Exact Test (FET). The time after entry in the RCT to LT evaluation and the duration of survival after evaluation and since entry were compared using the log-rank test. The MELD at time of LT was evaluated using the Wilcoxon rank test and the Child's risk class at LT evaluation using Fisher's exact test. Statistical significance was considered at the 0.05 level.

Characteristic	RCT No. 1			RCT No. 2		
	EST (n=106)	EPCS (n=105)	P Value	TIPS (n=78)	EPCS (n=76)	P Value
History						
Age (yrs):						
Mean/median	47.8/45	49.8/47	0.21	49.0/47	49.1/48	0.89
Range	23-75	28-82	0.61	30-84	31-73	0.62
n ≥ 70 yrs	7	9	0.61	1	2	0.35
Male gender, n (%)	81 (76)	81 (78)	0.87	56 (72)	60 (79)	0.65
Race, n (%):						
Caucasian	53 (50)	58 (55)	0.09	33 (42)	37 (49)	
Hispanic	50 (47)	39 (37)		39 (50)	34 (45)	
Other	3 (3)	8 (8)		6 (8)	5 (7)	
Cause of cirrhosis, n (%):			0.73			0.083
Alcoholism alone	58 (55)	54 (51)		29 (37)	24 (32)	
Hepatitis B or C alone	10 (9)	8 (8)		4 (5)	11 (14)	
Alcoholism and hepatitis	30 (28)	33 (31)		44 (56)	37 (49)	
Other	8 (8)	10 (9)		1 (1)	4 (5)	
Chronic alcoholism, n (%):			1.00			0.66
Years of alcoholism, mean (range)	22 (4-59)	25 (7-54)	0.56	21.6 (5-45)	21.6 (8-41)	0.97
Recent alcohol ingestion ≤ 7d, n (%)	55 (62)	57 (66)	0.99	42 (58)	34 (58)	0.44
Past history, n (%):						
Jaundice	61 (58)	58 (55)	0.78	32 (41)	42 (55)	0.11
Ascites	70 (66)	48 (46)	0.004*	40 (51)	53 (70)	0.022*
Portal-systemic encephalopathy	20 (19)	30 (29)	0.11	17 (22)	18 (24)	0.85
Delirium tremens in alcoholics	23 (26)	28 (31)	0.43	20 (28)	21 (34)	0.45
Physical examination, n (%):						
Jaundice	45 (42)	38 (36)	0.40	34 (44)	37 (49)	0.63
Ascites	65 (61)	54 (51)	0.17	37 (47)	46 (61)	0.11
Portal-systemic encephalopathy	19 (18)	19 (18)	1.0	19 (24)	17 (22)	0.8
Severe muscle wasting (2+ or 3+ on 0-3+ scale)	50 (47)	67 (64)	0.02*	40 (51)	49 (64)	0.11
Delirium tremens in alcoholics	2 (2)	2 (2)	1.00	1 (1)	3 (5)	0.33
PSE Index—median (interquartile range)	0 (0-0.15)	0 (0-0.15)	0.46	0 (0-0.15)	0 (0-0.16)	0.44
Child risk class, n (%):			0.71			0.98
A (5 to 8 points)	32 (30)	26 (25)		16 (21)	15 (20)	
B (9 to 11 points)	46 (43)	49 (47)		39 (50)	37 (49)	
C (12 to 15 points)	28 (26)	30 (29)		23 (29)	24 (32)	
Child risk class points, mean/median	10.1/10	10.0/10	0.76	10.2/10	10.6/11	0.26
	EST	EPCS	TOTAL	TIPS	EPCS	TOTAL
Referred for LT Evaluation, n (%)	7 (6.6)	6 (5.7)	13 (6.2)	8 (10.5)	2 (2.6)	10 (6.5)
Diagnosis of LT Candidates, n (%):						
Alcoholism	3 (2.8)	1 (1.0)	4 (1.9)	2 (2.6)	0	2 (1.3)
Hepatitis	2 (1.9)	0	2 (0.9)	0	0	0
Alcoholism and hepatitis	0	3 (2.9)	3 (1.4)	6 (7.7)	2 (2.6)	8 (5.2)
Cryptogenic	1 (0.9)	2 (1.9)	3 (1.4)	0	0	0
Autoimmune	1 (0.9)	0	1 (0.5)	0	0	0
Results of LT Evaluation:						
LT performed	4	0	4	4	0	4
LT approved but not done	2	1	3	0	0	0
LT denied	1	5	6	4	2	6
Reason for denial:						
Continued alcoholism	0	3	3	2	2	4
Continued drug abuse	0	1	1	0	0	0
Non-U.S. residence	1	0	1	0	0	0
Continued drug abuse and non-U.S. residence	0	1	1	2	0	2
Years after entry in RCT to final LT Evaluation—mean (range)	1.0 (0.04-2.35)	2.7 (0.02-6.74)	1.47 (0.02-6.74)	1.5 (0.75-1.5)	3.0 (2.0-3.5)	2.25 (0.75-3.5)
Approved for LT, n (%)	6 (5.6)	1 (1.0)	7 (3.3)	4 (5.1)	0	4 (2.6)
Years on waiting list—mean (range)	0.162 (0-0.59)	8.96 (n=1)		0.38 (0.5-0.7)	0	
Died on waiting list (time)	0	0	0	0	0	0
Survival after LT (n=) mean (range), yrs	0.204 (0.001-0.805)	N/A	0.204 (0.001-0.805)	0.4 (0.2-0.6)	N/A	0.4 (0.2-0.6)
Survival after evaluation, no LT mean (range), yrs (n=)	0.237 (0.047-0.586)	6.027 (0.017-12.73)	4.097 (0.017-12.73)	0.6 (0.2-0.8)	--	0.6 (0.2-0.8)
Survival since entry mean (range), yrs (n=)	1.266 (0.088-2.357)	8.720 (0.033-13.140)	4.706 (0.033-13.140)	1.9 (0.75-1.75)	--	1.9 (0.75-1.15)
MELD at LT evaluation—mean (range)	21.3 (7-39)	20.2 (7-36)	20.8 (7-39)	24 (20-30)	26 (22-32)	25 (20-32)

MELD at evaluation of LT patients mean (range)	20.8 (17-27)	--	20.8 (17-27)	24 (20-28)	--	24 (20-28)
Child class at LT evaluation:			TOTAL			TOTAL
A	0	0	0	0	0	0
B	1	4	5	0	0	0
C	6	2	8	8	2	10

*Statistically significant difference

Table 1: Clinical characteristics at time of study entry of patients with cirrhosis and bleeding esophageal varices randomized in RCT No. 1 to Endoscopic Sclerotherapy (EST) or Emergency Portacaval Shunt (EPCS) and in RCT No. 2 to TIPS or Emergency Portacaval Shunt (EPCS) with data on Liver Transplantation (LT).

Results

Patient characteristics

The clinical characteristics at the time of enrollment in the two RCTs are summarized in Table 1. The two groups in each RCT were similar in every important characteristic of cirrhosis and BEV. Over 80% of the patients were entered in the study by transfer from hospitals in the four-county referral area. In over three-fourths of the patients, the cause of cirrhosis was chronic alcoholism, often in combination with hepatitis. The distribution of patients in Child risk classes, determined by Campbell's quantitative modification [22] of the criteria originally proposed by Child and Turcotte [23] was almost identical in the two groups, with 20 to 30% in risk class A, 43% and 50% in risk class B, and 26% to 29% in risk class C. The overall Child risk class points in the two groups of patients were essentially identical. Liver biopsies provided histologic proof of cirrhosis in all patients. Upper endoscopy demonstrated sizable esophageal varices in all patients, with active bleeding or evidence of recent acute bleeding in over 90%. Almost two-thirds of patients had serologic evidence of hepatitis B or C.

Rapidity of therapy

Table 3 provides data on rapidity of BEV therapy. The mean and median times from onset of bleeding to entry in the San Diego BEV Study were <20 hours in all groups of patients. The mean and median

times from onset of bleeding to the start of EST or EPCS or TIPS were <24 hours. After initial contact at UCSD Medical Center primary therapy was started in <8 hours in most patients and always in less than 24 hours, clearly a reflection of the rapidity with which the diagnostic workup was performed. The mean time from initial contact to primary therapy was always less than 24 hours. Patients who were transferred to UCSD Medical Center from outside facilities on average spent <12 hours in the referring hospitals. Before entry into the study, active bleeding had been observed within 4 hours in 84% of the patients. Without doubt, the study involved evaluation of emergency treatment of acute BEV.

Control of variceal bleeding

Data on control of variceal bleeding by EEST, TIPS, and EPCS are shown in Table 4. In an effort to obtain temporary control of bleeding while the diagnostic workup was in progress, patients in RCT No. 1 were given a continuous IV infusion of vasopressin, and patients in RCT No. 2 received octreotide intravenously as well as endoscopic sclerotherapy. With regard to immediate and long-term control of variceal bleeding, there was a striking and highly significant difference between EEST and EPCS in RCT No. 1, and between TIPS and EPCS in RCT No. 2 (p<0.001). Excluding indeterminate deaths within the first 3 weeks from causes other than bleeding, EEST achieved long-term control of bleeding in only 20% of patients, and TIPS achieved long-

Findings	RCT NO. 1—EST vs. EPCS			RCT NO. 2—EPCS vs. TIPS		
	EST (n=106)	EPCS (n=105)	P value	EPCS (n=76)	TIPS (n=78)	P value
Cirrhosis on liver biopsy, n (%)	106 (100)	105 (100)	1.0	76 (100)	78 (100)	1.0
Esophageal varices on endoscopy, n (%)	106 (100)	105 (100)	1.0	76 (100)	78 (100)	1.0
Size 2+ to 4+ (on scale of 0-4+), n (%)	102 (96)	105 (100)	0.68	71 (92)	69 (88)	0.4
Active bleeding, n (%)	41 (39)	29 (28)	0.11	37 (49)	50 (52)	0.5
Clot on varices, n (%)	53 (50)	51 (49)	0.89	45 (63)	40 (52)	0.18
Red color signs on varices, n (%)	67 (63)	66 (63)	1.00	34 (47)	35 (45)	1.0
Gastric varices on endoscopy, n (%)	19 (18)	17 (16)	0.86	25 (33)	28 (36)	0.74
Portal hypertensive gastropathy, n (%)	23 (22)	22 (21)	1.00	46 (61)	38 (49)	0.15
Laboratory blood tests, median/mean (range)						
Lowest hemoglobin, g/dL	8.0/8.4 (2.0-8.1)	8.0/8.0 (2.6-11.9)	0.40	7.5/7.4 (2.3-13.7)	7.9/7.9 (2.8-22.5)	0.17
Lowest hematocrit, %	23.4/22.8 (6.0-39.4)	23.5/23.7 (11.0-35.4)	0.46	22.3/21.85 (2-36.8)	23/22.6 (7.5-32.8)	0.32
Lowest platelet count, 1,000/mm ³	87/97.6 (25-340)	76/95.4 (15-268)	0.36	78.0/88.1 (3-328)	77.5/92.7 (25-296)	0.56
Serum bilirubin, mg/dL						
Direct	0.5/1.1 (0.1-12.0)	0.4/0.7 (0.1-3.7)	0.12	0.75/0.91 (0.1-3.7)	0.65/1.29 (0.1-14.7)	0.89
Total	2.4/3.5 (0.6-15.2)	1.9/2.7 (0.4-14.8)	0.25	2.25/2.66 (0.9-7.5)	2.15/3.18 (0.5-25.4)	0.89
Albumin, g/dL	2.6/2.6 (1.4-3.9)	2.5/2.6 (1.4-4.5)	0.49	2.5/2.78 (1.2-2.4)	2.4/2.45 (1.6-3.5)	0.43
Aspartate transaminase, IU/L	73/116 (16-1,359)	66/88 (16-582)	0.37	65/83 (24-351)	67/178 (16-4,010)	0.41
Alanine transaminase, IU/L	35/54 (11-432)	36/47 (9-582)	0.56	32/43 (13-230)	34/72 (9-645)	0.52
Alkaline phosphatase, IU/L	86/95 (1.3-367)	79/88 (29-218)	0.20	75/90 (12-476)	75/88 (32-299)	0.9
International normalized ratio	1.3/2.8 (0.6-5.8)	1.3/1.4 (1.1-2.6)	0.39	1.4/1.5 (1.1-4.1)	1.4/1.5 (1.1-3.0)	0.94
Arterial ammonia, μmol/L	76/93 (33-253)	75/92 (26-497)	0.83	85/122 (32-2,002)	88/97 (24-251)	0.65
Creatinine, mg/dL	0.8/1.4 (0.4-10)	0.8/1.0 (0.5-2.7)	0.89	0.8/0.92 (0.4-2.9)	0.8/0.91 (0.4-2.2)	0.94
Blood urea nitrogen, mg/dL	22/27 (7-85)	21/23 (6-69)	0.22	20/23.1 (5-91)	19/21.1 (4-68)	0.43
Glucose, mg/dL	133/152 (74-548)	135/157 (60-368)	0.44	128/146 (11-389)	143/154 (89-367)	0.17
Blood alcohol 0.01% or higher, n (%)	9 (8)	13 (12)	0.29	7 (9)	6 (8)	0.78
Blood alpha fetoprotein, ng/mL, mean (range)	4 (0-18)	4 (0-10)	0.84	4 (0-118)	4 (0-181)	0.98
Positive HBV or HCV serology, n (%)	37 (35)	44 (42)	0.32	47 (62)	49 (63)	1

EST-Endoscopic Sclerotherapy; EPCS- Emergency Portacaval Shunt; HBV- Hepatitis B Virus; HCV- Hepatitis C Virus; TIPS-Transjugular Intrahepatic Portosystemic Shunt

Table 2: Findings on liver biopsy, endoscopy, and laboratory blood tests at time of study entry in patients with cirrhosis and bleeding esophageal varices randomized in RCT No. 1 to endoscopic sclerotherapy or emergency portacaval shunt and in RCT No. 2 to TIPS or emergency portacaval shunt.

	RCT NO. 1—EST vs. EPCS					RCT NO. 2—EPCS vs. TIPS				
	EST (n=106)		EPCS (n=105)		P Value	EPCS (n=76)		TIPS (n=78)		P Value
Hours	Median/Mean	Range	Median/Mean	Range		Median/Mean	Range	Median/Mean	Range	
Onset bleeding to study entry	12/19.8	0-144	16/19	0-95	0.30	20/25.4	0-112	17/24.2	0.5-84	0.56
Onset bleeding to primary therapy	15/23.3	3-147	19/21.5	2.6-100	0.056	27.5/35.9	8-131.7	34.2/39.0	11.1-99.4	0.08
Study entry to primary therapy	2.5/3.1	0.8-8	3.4/4.4	1.4-24.3	<0.001*	9.5/10.2	2-30.1	14.6/14.7	2.3-38.4	<0.001*
n>8 h	0		3			3		76 (97)		1.0
%>8 h	0		2.9			3.9		68 (87)		0.5
Transfer patients, n (%)	71 (67)		80 (76)		0.17	63 (83)		68 (87)		0.5
Onset of bleeding to entry in referring hospital	4.05/10.4	0-127	3.75/9.7	0-83.6	0.92	6.3/11.9	0-120	5.7/9.8	0-62	0.72
Entry into referring hospital to study entry	7.2/11.8	1.5-53	8.4/11.6	0-53	0.56	13.0/18.4	2.2-110	10.5/16.4	2.6-65.3	0.42
Last observation of bleeding to study entry	0/1.9	0-32	0/2.5	0-30	0.76	0/1.6	0-32	0/3.6	0-84	0.35
≤4 h, % of group	84		84		0.94	67 (88)		63 (81)		0.27
>4 h, % of group	16		16		1.00	9 (12)		15 (19)		

*Statistically significant difference

EPCS-Emergency Portacaval Shunt; EST- Endoscopic Sclerotherapy; TIPS-Transjugular Intrahepatic Portosystemic Shunt

Table 3: Rapidity of therapy for patients with cirrhosis and bleeding esophageal varices in RCT No. 1 (endoscopic sclerotherapy versus emergency portacaval shunt) and RCT No. 2 (TIPS versus emergency portacaval shunt).

	RCT NO. 1			RCT NO. 2		
	EST (n=106)	EPCS (n=105)	P Value	EPCS (n=76)	TIPS (n=78)	P Value
Control of bleeding, n (%)						
Temporary during workup						
Received vasopressin or octreotide intravenously	95 (90)	80 (76)	0.012*	60 (83)	71 (92)	0.13
Bleeding at start of vasopressin or octreotide infusion	47 (49)	55 (69)	0.014*	40 (67)	44 (71)	0.59
Bleeding decreased or stopped	36 (77)	38 (69)	0.51	19 (48)	24 (58)	0.66
Permanent by EST or EPCS (RCT No. 1) or by TIPS (RCT No. 2)						
Indeterminate, nonbleeding death ≤14 d	4 (4)	12 (11)	0.040*	16 (21)	8 (10)	0.078
Successful control excluding indeterminates for at least						
14 d	22 (21)	93 (100)	<0.001*	60 (100)	58 (83)	<0.001*
30 d	20 (20)	89 (100)	<0.001*	57 (95)	56 (80)	0.017*
>30 d	20 (20)	89 (100)	<0.001*	57 (95)	54 (77)	0.005*
Declaration of primary therapy failure, n (%)	81 (79)	0 (0)	<0.001*			
Required ≥ 6 U PRBC in first 7 d	15 (19)	--		0 (0)	9 (13)	0.003*
Required ≥ 8 U PRBC in any 12 mo	47 (58)	--		2 (3)	33 (47)	<0.001*
Recurrent variceal bleeding after variceal obliteration was declared	27 (33)	--		0 (0)	32 (46)	<0.001*
More than one criterion for failure	8 (10)	--		0 (0)	19 (27)	<0.001*
PRBC transfusion, U, mean/median (range)						
Index hospitalization						
Before primary therapy	4.5/4 (2-12)	5.8/5 (2-17)	<0.001*	5/5.6 (0-14)	5/6.3 (0-30)	0.83
During primary therapy	0.6/0 (0-7)	6.3/3 (0-68)	<0.001*	3.5/5.4 (0-32)	0/0.4 (0-6)	<0.001*
"Catch-up" after primary therapy	0.2/0 (0-4)	1.2/0 (0-21)	0.001*	0/0.8 (0-15)	0/0.2 (0-4)	0.056
Posttherapy bleeding						
Variceal	4.4/0 (0-37)	0/0 (0-0)	<0.001*	0/1.1 (0-46)	0/2.6 (0-29)	<0.001*
Nonvariceal	0.3/0 (0-11)	1.8/0 (0-29)	0.059	0/1.1 (0-21)	0/0.1 (0-6)	0.020*
Total PRBC units	10.0/7 (2-44)	15.0/10 (2-81)	<0.001*	9/14.0 (0-85)	7/9.8 (2-42)	0.010*
Readmissions for bleeding						
Variceal bleeding	6.8/2 (0-60)	0.4/0 (0-26)	<0.001*	0/0.2 (0-14)	6/6.6 (0-36)	<0.001*
Nonvariceal bleeding	3.8/0 (0-38)	3.5/0 (0-33)	0.23	0/0.4 (0-10)	0/0.5 (0-11)	0.62
Total PRBC units	10.6/7 (0-60)	3.9/0 (0-33)	<0.001*	0/06.9 (0-14)	6/7.0 (0-36)	<0.001*
Total PRBC units for variceal bleeding	15.8/14 (2-64)	13.6/10 (2-73)	0.037*	8/11.7 (0-85)	14/15 (3-47)	<0.001*
Overall survival (Pr/95% CI)			<0.001*			<0.001*
30-d	0.88 (0.81, 0.94)	0.87 (0.80, 0.93)		0.77 (0.68, 0.87)	0.78 (0.70, 0.88)	0.96
1-yr	0.72 (0.64, 0.81)	0.81 (0.74, 0.89)		0.75 (0.65, 0.85)	0.55 (0.45, 0.67)	0.022*
2-yr	0.54 (0.45, 0.64)	0.77 (0.70, 0.86)		0.68 (0.58, 0.79)	0.49 (0.39, 0.61)	0.022*
3-yr	0.44 (0.36, 0.55)	0.75 (0.67, 0.84)		0.65 (0.55, 0.77)	0.36 (0.27, 0.48)	0.001*
4-yr	0.35 (0.27, 0.45)	0.74 (0.66, 0.83)		0.63 (0.53, 0.75)	0.23 (0.15, 0.35)	<0.001*
5-yr	0.21 (0.14, 0.30)	0.73 (0.65, 0.82)		0.61 (0.51, 0.73)	0.20 (0.13, 0.31)	<0.001*
7-yr				0.52 (0.41, 0.66)	0.15 (0.09, 0.28)	<0.001*
10-yr	0.09 (0.05, 0.17)	0.46 (0.37, 0.56)		--	--	
15-yr	0.09 (0.05, 0.17)	0.46 (0.37, 0.56)		--	--	
Median survival, yr (95% CI)	2.48 (1.58, 3.76)	6.17 (5.60, 10.37)		>10 (5.1 >10)	1.99 (0.52, 2.8)	
Survival by Child risk class (Pr/95% CI)						
5-yr Child class (PR/95% CI)						
A	0.38 (0.24, 0.59)	0.89 (0.83, 1.00)	0.003*	0.85 (0.68, 1)	0.38 (0.20, 0.71)	0.006*
B	0.15 (0.08, 0.30)	0.76 (0.64, 0.89)	<0.001*	0.65 (0.51, 0.82)	0.22 (0.12, 0.41)	<0.002*
C	0.11 (0.04, 0.31)	0.57 (0.41, 0.78)	0.005*	0.42 (0.26, 0.67)	0.04 (0.01, 0.30)	0.016*
10-yrs Child class (PR/95% CI)						
A	0.18, (0.08, 0.38)	0.62 (0.45, 0.83)	0.003*	0.76 (0.55, 1)	0.30 (0.20, 0.71)	0.008*
B	0.07 (0.02, 0.20)	0.45 (0.33, 0.61)	<0.001*	0.51 (0.36, 0.71)	0.15 (0.06, 0.41)	0.003*
C	0.04 (0.01, 0.25)	0.33 (0.20, 0.55)	0.005*	0.42 (0.26, 0.67)	0.04 (0.01, 0.30)	0.016*
Median survival, yr (95% CI)						
A	4.62 (4.08, 6.34)	10.43 (>5.92)	0.003*	>9.37 (>9.37 >9.37)	3.46 (0.51, 8.05)	0.008*
B	2.61 (1.65, 3.96)	6.19 (>5.44)	<0.001*	>9.80 (5.09 >9.80)	2.12 (1.03, 3.00)	<0.001*
C	0.58 (0.12, 2.36)	5.30 (0.70, 10.16)	0.005*	1.25 (0.06 >9.66)	0.08 (0.04, 1.99)	0.016*

Survival by direct UCSD admission versus transfer from outside UCSD (Pr/95% CI)						
Direct UCSD admission	0.38 (0.24, 0.59)	0.89 (0.83, 1.00)	0.003*	0.85 (0.68, 1)	0.38 (0.20, 0.71)	0.006*
5 yr	0.15 (0.08, 0.30)	0.76 (0.64, 0.89)	<0.001*	0.65 (0.51, 0.82)	0.22 (0.12, 0.41)	<0.002*
7 yr	0.11 (0.04, 0.31)	0.57 (0.41, 0.78)	0.005*	0.42 (0.26, 0.67)	0.04 (0.01, 0.30)	0.016*
10 yr						
Transfer from outside UCSD	0.18, (0.08, 0.38)	0.62 (0.45, 0.83)	0.003*	0.76 (0.55, 1)	0.30 (0.20, 0.71)	0.008*
5 yr	0.07 (0.02, 0.20)	0.45 (0.33, 0.61)	<0.001*	0.51 (0.36, 0.71)	0.15 (0.06, 0.41)	0.003*
7 yr	0.04 (0.01, 0.25)	0.33 (0.20, 0.55)	0.005*	0.42 (0.26, 0.67)	0.04 (0.01, 0.30)	0.016*
10 yr						
Mean survival, yr (95% CI)	4.62 (4.08, 6.34)	10.43 (>5.92)	0.003*	>9.37 (>9.37 >9.37)	3.46 (0.51, 8.05)	0.008*
Direct UCSD admission	2.61 (1.65, 3.96)	6.19 (>5.44)	<0.001*	>9.80 (5.09 >9.80)	2.12 (1.03, 3.00)	<0.001*
Transfer from outside UCSD	0.58 (0.12, 2.36)	5.30 (0.70, 10.16)	0.005*	1.25 (0.06 >9.66)	0.08 (0.04, 1.99)	0.016*
Survival by direct UCSD admission versus transfer from outside UCSD (Pr/95% CI)			0.48			0.13
Direct UCSD admission						
5 yr	0.17 (0.08, 0.36)	0.58 (0.42, 0.80)		0.46 (0.26, 0.83)	0.20 (0.06, 0.69)	
7 yr	--	--		0.31 (0.14, 0.70)	0.10 (0.02, 0.64)	
10 yr	0.11 (0.05, 0.29)	0.52 (0.27, 0.66)		--	--	
Transfer from outside UCSD						
5 yr	0.24 (0.16, 0.36)	0.79 (0.70, 0.88)		0.64 (0.53, 0.77)	0.20 (0.12, 0.32)	
7 yr	--	--		0.57 (0.46, 0.72)	0.17 (0.10, 0.30)	
10 yr	0.08 (0.03, 0.18)	0.45 (0.36, 0.58)				
Mean survival, yr (95% CI)						
Direct UCSD admission	2.71 (0.72, 4.51)	5.28 (>2.80)		1.25 (0.04 >9.79)	1.03 (0.49 >7.13)	
Transfer from outside UCSD	2.45 (1.59, 3.76)	6.25 (5.81, 11.03)		>10 (5.18 >10)	1.99 (0.51, 3.0)	
Rescue portacaval shunt in EST group—effect on median survival, yr (95% CI) and rescue portacaval shunt in TIPS group						
Successful EST (n=21) or TIPS (n=15)	2.76 (1.52, 7.35)	--	0.48	--	3.75 (1.15 >7.18)	0.95
Failed EST (n=81) or failed TIPS (n=55)	2.71 (1.65, 3.92)	--			2.04 (0.92, 2.88)	0.98
Rescue shunt-failed EST (n=50) or rescue shunt in failed TIPS (n=8)	3.01 (1.65, 4.34)	--	0.098	--	>8.06 (3.93 >8.06)	0.98
No rescue shunt-failed EST (n=31) or failed TIPS (n=39)	2.36 (0.72, 4.34)	--			1.03 (0.50, 2.67)	
Overall survival: rescue shunt (n=50) versus primary EPCS (n=105) in RCT No. 1 and rescue shunt (n=8) versus primary EPCS (n=64) in RCT No. 2	3.01 (1.65, 4.34)	6.18 (5.61, 10.38)	<0.001*	>10 (5.1 >10)	>8.06 (3.93 >8.06)	0.98
Postoperative survival: rescue shunt (n=50) versus primary EPCS (n=105)	1.99 (1.34, 3.73)	6.18 (5.61, 10.38)	<0.001*	>10 (5.1 >10)	>8.04 (3.08 >8.04)	0.67
10-yr Child class (Pr/95% CI)						
A	0.18 (0.08, 0.38)	0.62 (0.45, 0.83)	0.003*			
B	0.07 (0.02, 0.20)	0.45 (0.33, 0.61)	<0.001*			
C	0.04 (0.01, 0.25)	0.33 (0.20, 0.55)	0.005*			
Median survival, yr (95% CI)						
A	4.62 (4.08, 6.34)	10.43 (>5.92)	0.003*	>9.37 (>9.37 >9.37)	3.46 (0.51, 8.05)	0.008*
B	2.61 (1.65, 3.96)	6.19 (>5.44)	<0.001*	>9.80 (5.09 >9.80)	2.12 (1.03, 3.00)	<0.001*
C	0.58 (0.12, 2.36)	5.30 (0.70, 10.16)	0.005*	1.25 (0.06 >9.66)	0.08 (0.04, 1.99)	0.016*
Survival by direct UCSD admission versus transfer from outside UCSD (Pr/95% CI)						
Direct UCSD admission						
5 yr	0.17, (0.08, 0.36)	0.58 (0.42, 0.80)	0.48	0.46 (0.26, 0.83)	0.20 (0.06, 0.69)	0.13
10 yr	0.11 (0.05, 0.29)	0.52 (0.27, 0.66)				
Transfer from outside UCSD						
5 yr	0.24 (0.16, 0.36)	0.79 (0.70, 0.88)		7-yr: 0.31 (0.14, 0.70)	0.10 (0.02, 0.64)	
10 yr	0.08 (0.03, 0.18)	0.45 (0.36, 0.58)		0.64 (0.53, 0.77)	0.20 (0.12, 0.32)	
Mean survival, yr (95% CI)						
Direct UCSD admission	2.71 (0.72, 4.51)	5.28 (>2.80)		1.25 (0.04 >9.79)	1.03 (0.49, >7.13)	
Transfer from outside UCSD	2.45 (1.59, 3.76)	6.25 (5.81, 11.03)		>10 (5.18 >10)	1.99 (0.51, 3.0)	
Rescue portacaval shunt in EST group (RCT No. 1) Or TIPS (RCT No. 2)—effect on median survival, yr (95% CI)						
Successful EST (n=21) or TIPS (n=15)	2.76 (1.52, 7.35)	--	0.48	--	3.75 (1.15, >7.18)	0.95
Failed EST (n=81) or TIPS (n=55)	2.71 (1.65, 3.92)	--			2.04 (0.92, 2.88)	0.001*
Rescue shunt-failed EST (n=50) or failed TIPS (n=8)	3.01 (1.65, 4.34)	--	0.098	--	>8.06 (3.98, >8.06)	0.98
No rescue shunt-failed EST (n=31) or failed TIPS (n=39)	2.36 (0.72, 4.34)	--			>8.06 (3.93, >8.06)	
Overall survival: rescue shunt (n=50) versus primary EPCS (n=105) in RCT No. 1, rescue shunt (n=8) versus primary EPCS in RCT No. 2	3.01 (1.65, 4.34)	6.18 (5.61, 10.38)	<0.001*	>10 (5.1 >10)	>8.06 (3.98, >8.06)	0.98
Postoperative survival: rescue shunt (n=50) versus primary EPCS (n=105) in RCT No. 1, rescue shunt (n=8) versus primary EPCS (n=76) in RCT No. 2	1.99 (1.34, 3.73)	6.18 (5.61, 10.38)	<0.001*	>10 (5.1 >10)	>8.04 (3.08, >8.04)	0.67

Pr-probability; PRBC, Packed Red Blood Cells; UCSD-University of California-San Diego.

*Statistically significant difference

Table 4: Control of bleeding and survival in RCT No. 1 (endoscopic sclerotherapy versus emergency portacaval shunt) and in RCT No. 2 (emergency portacaval shunt versus TIPS) in patients with bleeding esophageal varices.

term control of bleeding in only 22%. In contrast, EPCS promptly and permanently controlled bleeding in 100% of patients in RCT No. 1, and in 97% of patients in RCT No. 2. Failure of EEST in RCT No. 1 and of TIPS in RCT No. 2 was declared according to the criteria established by the study protocol.

The requirement for PRBC transfusions reflects the success or failure of treatment of BEV and is summarized in Table 4. In each RCT, patients in the EPCS group required almost no blood transfusions for recurrent BEV. In contrast, patients treated by EEST and those treated by TIPS had repeated readmissions to the hospital for recurrent BEV that required blood transfusions.

Survival

Table 4 summarizes data on survival and Figure 2 shows long-term Kaplan-Meier estimated survival plots for EEST and EPCS in RCT No. 1, and Figure 3 shows estimated survival for TIPS and EPCS in RCT No. 2. The 30-day survival rates of 88% and 87%, respectively, for EEST and EPCS in RCT No. 1, and 77% and 78% for EPCS and TIPS in RCT No. 2 were essentially identical. Subsequently, however, there were highly significant differences of the two study groups at all time intervals in each RCT. In RCT No. 1, the 1-, 5-, 10-, and 15-years survival rates in the EEST group were 72%, 21%, 9%, and 9%, respectively, and in the EPCS group were 81%, 73%, 46%, and 46%, respectively ($p < 0.001$). In RCT No. 2, the 1-, 3-, 5-, and 7-year survival rates in the TIPS group were 55%, 36%, 20%, and 15%, respectively, and in the EPCS group were 75%, 65%, 61%, and 52%, respectively ($p < 0.001$). Median survival following TIPS was 1.9 years while median survival following EPCS was greater than 10 years. As anticipated, survival rates were related to effectiveness in control of bleeding as well as to the severity of liver disease as expressed by Child risk class upon entry in each RCT, and shown in Table 4 and Figure 2.

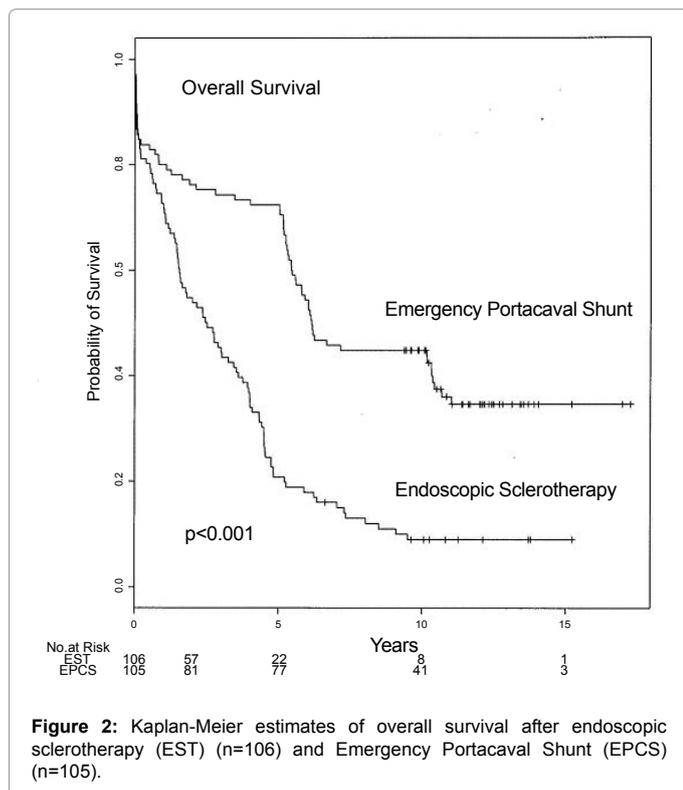


Figure 2: Kaplan-Meier estimates of overall survival after endoscopic sclerotherapy (EST) (n=106) and Emergency Portacaval Shunt (EPCS) (n=105).

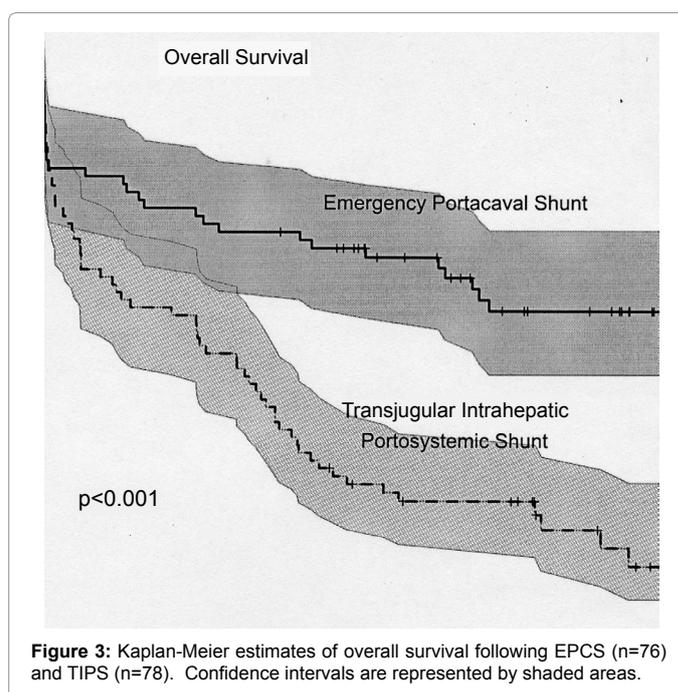


Figure 3: Kaplan-Meier estimates of overall survival following EPCS (n=76) and TIPS (n=78). Confidence intervals are represented by shaded areas.

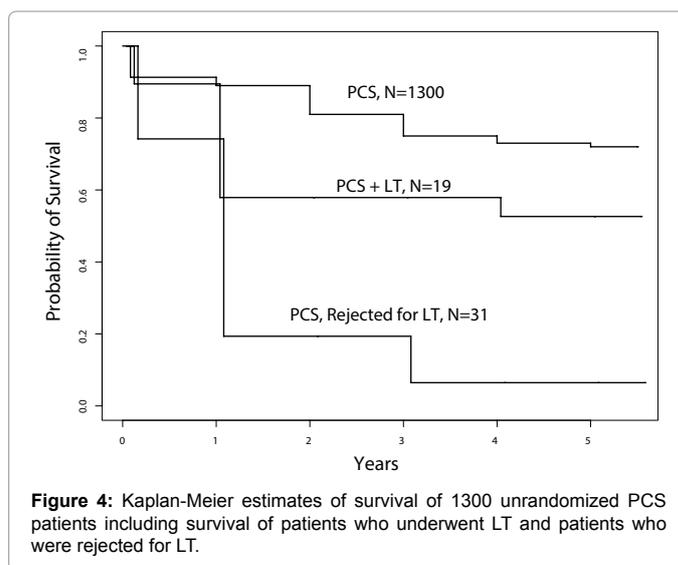


Figure 4: Kaplan-Meier estimates of survival of 1300 unrandomized PCS patients including survival of patients who underwent LT and patients who were rejected for LT.

In striking contrast, the 1- and 5-years LT survival rates were 0.68% and 0, respectively, in RCT No. 1, and 0.4% and 0 in RCT No. 2.

Operative EPCS data

Direct side-to-side PCS was performed in 94% of the 105 patients randomized to EPCS in RCT No. 1, and in 93% of the 76 patients randomized to EPCS in RCT No. 2. The remaining 6-7% of patients received a direct end-to-side PCS. Mean operative time for EPCS in RCT No. 1 was 4.0 hours and in RCT No. 2 was 3.8 hours. Estimated blood loss during EPCS in these patients with active variceal bleeding, averaged 3,094 ml in RCT No. 1 and 1,600 ml in RCT No. 2. Accordingly, the operative requirement for PRBC transfusion in these actively bleeding patients was 6.3 units in RCT No. 1 and 3.0 units in RCT No. 2. The PV-IVC pressure gradient before the shunt averaged 244 mm saline in RCT No. 1 and 241 mm saline in RCT No. 2. EPCS reduced the PV-IVC gradient to a mean 17 mm in RCT No. 1 and 20

mm in RCT No. 2. EPCS promptly eliminated portal hypertension in all patients and stopped the bleeding. Importantly, the PCS remained permanently patent throughout life in 98% of the patients in RCT No. 1 and 97% of the patients in RCT No. 2.

Operative TIPS data

Median TIPS operative time was 3 hrs (range 1.25 to 25 hrs). The median PV-IVC pressure gradient before TIPS was 22 mmHg (range 10 to 42 mmHg), and after TIPS it was reduced to 7 mmHg (range 0 to 17 mmHg). The mean number of Wallstents placed in the TIPS was 1.24 (range 0 to 3), with a diameter of 12 mm in 96% of patients and 10 mm in 4% and a length of 9 cm in 69% of patients and 6 cm in the remainder. Balloon diameter was 10 or 12 mm in 96% of subjects. The median number of needle passes required to enter the PV was 5 (range 1 to 40). During the TIPS procedure, the mean requirement for PRBC transfusions was 0.53 units (range 0 to 6). At the conclusion of the procedure, TIPS was considered a technical success in 87% of the patients, a failure in 11%, and indeterminate in 2.7%.

TIPS technical success or failure during follow-up

TIPS-specific follow-up by color Doppler sonography, angiography, EGD, and regular clinical examinations was conducted rigorously. Since almost one-fourth of the patients died during the first 3 weeks postoperatively, the durability of TIPS was analyzed in the patients who survived for 21 days or more. TIPS stenosis or occlusion was demonstrated in 38 (84%) of these patients. They developed a mean 2.1 episodes of TIPS stenosis or occlusion (standard deviation 1.80, range 0-9). TIPS stenosis or occlusion was demonstrated 46 times in the first post-entry year, 26 times in the second year after entry, and 26 times in patients who survived for three or more years. Twenty-four of these 38 patients with TIPS malfunction, or 63%, underwent revision of the TIPS by balloon angioplasty or insertion of one or more additional stents. The revisions failed in 80% of the patients, and success was indeterminate in an additional 8%. The durability of TIPS was disappointing.

Portal-systemic encephalopathy (PSE)

The important complication of PSE was analyzed and reported in detail in our recent publications, which should be consulted by the reader [24,25]. Recurrent PSE was defined as two or more episodes of PSE after primary therapy in patients who survived 30 days and left the hospital. In RCT No. 1, recurrent PSE developed in 35% of the EEST group and 15% of the EPCS group, a highly significant difference ($p=0.001$). In RCT No. 2, recurrent PSE developed in 61% of the patients treated by TIPS, compared to 21% of the patients who underwent EPCS. The three-fold greater incidence of PSE in the TIPS group was highly significant ($p<0.001$).

Direct cost of care

The total post-index charges were significantly greater in patients who were treated by EEST or TIPS compared to those who underwent EPCS ($p<0.001$), and the total overall charges for emergency and long-term care required over a number of years were greater in patients who received emergency followed by long-term repetitive EEST, or by TIPS related to length of survival and, therefore, days or years during which care was required. EPCS was significantly less expensive than EEST or TIPS in every aspect of care except for the index admission. Charges for post-index care per year in the EEST and EPCS groups, respectively, were a mean \$108,500 versus \$25,100 ($p<0.001$). Total overall charges for care of patients who entered RCT No. 1 were a mean \$168,100 per year in the EEST group, versus \$39,400 per year in the EPCS group ($p<0.001$).

Of particular note were the charges in patients who failed EEST and underwent a rescue PCS. Charges for such patients were significantly higher than the charges required by EEST patients who did not have a rescue shunt as well as by the patients who underwent EPCS. This finding is noteworthy because the main use of surgical shunts in recent years in the USA and abroad has been as elective rescue treatment for failure of endoscopic therapy and other forms of treatment of esophageal varices. Our study indicates that such use of surgical shunts is not only substantially less effective than EPCS, but also is much more costly.

The reasons why EPCS was less costly than EEST and TIPS are very likely a consequence of differences in effectiveness of emergency treatment of BEV. The most important determinants of effectiveness of therapy are survival rate, control of bleeding, and incidence of recurrent PSE. As we have observed in our recent reports, compared to EEST and TIPS, EPCS produced a significantly greater survival rate, was much more effective in controlling bleeding, and was followed by less than one half the incidence of PSE.

Liver transplantation in RCT No. 1 and RCT No. 2

Of the 211 patients in RCT No. 1, only 13 (6%) were ultimately referred for LT, mainly because of progressive liver failure; only 7 (3%) were approved for LT and only 4 (2%) underwent LT. The 1- and 5-years LT survival rates were 0.68% and 0, respectively, compared with 81% and 73% survival rates, respectively, after EPCS. Of the 154 patients in RCT No. 2, only 10 (6.5%) were ultimately referred for LT, mainly because of progressive liver failure. Eight of the 10 patients were in the TIPS group. Only 4 (2.6%) were approved for LT and only these 4 (2.6%) underwent LT. Thus, only 2% of the total 365 randomized patients with BEV underwent LT. The 1- and 5-years LT survival rates in RCT No. 2 were 0.4% and 0, respectively, compared with 75% and 61% survival rates, respectively, after EPCS.

We concluded that if bleeding is permanently controlled, as occurred invariably following EPCS, cirrhotic patients with BEV seldom require LT. Should LT be required in patients with PCS, although technically more demanding, numerous studies have shown that PCS does not increase mortality or complications. Our experience confirmed that conclusion.

Table 1 summarizes data on the 23 patients who were ultimately referred for LT from among the 365 patients (6%) randomized in RCT No. 1 and RCT No. 2. Figure 2 shows Kaplan-Meier survival plots of the patients who underwent LT and the patients who were evaluated for but did not undergo LT, and compares their survival curves with the Kaplan-Meier curves showing the overall survival of patients who received EST or TIPS or EPCS in the RCTs. As was true of the overall survival of patients in the EPCS group, patients from this group who were evaluated for LT lived more than 8 years, even though they did not undergo LT. In contrast, as was true of the EST and TIPS groups in general, patients from these groups who were evaluated for or underwent LT had a mean survival of 1.5 years or less.

Liver transplantation in the unrandomized portacaval shunt patients

All 1300 unrandomized patients had cirrhosis proven by biopsy and bleeding varices proven by endoscopy. The cause of cirrhosis in 85% of the patients was chronic alcoholism without or with serologically proven chronic viral hepatitis. Quantitative Child's risk classes were A, 11%; B, 50%; and C, 39%. Serious risk factors on admission or past history were ascites in 64%, jaundice in 58%, PSE in 36%, and severe muscle wasting in 49%. 90% of the patients had end-stage cirrhosis.

Indications for LT after PCS were declining liver function in the presence of end-stage cirrhosis. Only patients who had been abstinent for 6 or more months were accepted as candidates for LT.

Only 50 of the 1300 patients (3.8%) were referred for LT. 19 of the 1300 (1.5%), all in Child's class B (26%) or C (74%), underwent LT. 12 were EPCS patients and 7 were elective PCS patients. The remaining 31 patients were rejected for LT because of resumption of alcoholism, substance abuse, infection, and various other serious comorbidity.

The 30-days, 5-years, and 10-years survival rates, respectively, were 83%, 67%, and 67% after emergency PCS, and 98%, 76%, and 71% after elective PCS. Following LT, the 30-days and 5-years survival rates were 89% and 53%, respectively. The 5-years survival rate of the 31 patients who were proposed but rejected for LT was only 7%. PCS did not increase the mortality rate or complications of subsequent LT compared with the reports in the literature of that time period and with a large group of unshunted cirrhotic patients who underwent LT. Figure 4 compares 5-years Kaplan-Meier survival plots of the 1300 PCS patients with both the PCS patients who underwent LT and the PCS patients who were rejected for LT.

Regular follow-up was achieved in 100% of the patients for 5 years and 97% for 10 years. During those time periods, all but 2 of the 1300 patients remained free of recurrent BEV and the PCS remained permanently patent in all but 2 patients (99.8%). Recurrent PSE was observed in 10% of the patients. Liver function improved in 76% of the patients and, after 5 years, only 6% of the patients were in Child's class C, compared to 39% on admission.

Discussion

The two RCTs of emergency treatment of BEV that are the substance of this report were unique in a number of important respects. They involved a large number of unselected, consecutive patients ("all comers") with acute BEV, 211 in RCT No. 1 and 154 in RCT No. 2. No comparable studies of similar magnitude have been reported. Unlike other studies, 30% of the patients were in Child class C with advanced cirrhosis. Both RCTs were community-wide endeavors in which, by prior agreement, 72% to 82% of the patients were rapidly referred to UCSD Medical Center from hospitals in four area counties that have a population of 8.5 millions. The entire diagnostic workup, including emergency upper endoscopy, was completed at the bedside in the ICU within less than 8 hr of study entry. Definitive therapy was undertaken within 15 hrs of initial contact with the UCSD staff. EPCS was performed by two senior faculty surgeons with extensive operative experience with portacaval shunt. EEST was performed by board-certified attending faculty gastroenterologists with a long experience in endoscopic therapy. TIPS was performed by senior attending faculty interventional radiologists with vast experience in TIPS. The type of EPCS was a direct portacaval shunt, side-to-side in almost all patients, end-to-side in a few. Cirrhosis was confirmed by liver biopsy in 100% of patients. Regular follow-up was accomplished in 100% of patients and lasted for 10 or more years or until death in RCT No. 1, and for 5 to 10 years or until death in RCT No. 2. No comparable studies with similar long follow-up have been reported.

EPCS by direct anastomosis between the portal vein and IVC permanently controlled BEV in 95% of patients or more and resulted in long-term survival that was markedly greater than that obtained by TIPS or EST. These results are similar to our recent and past experience with EPCS [8-17]. Moreover, the survival rate is higher than that reported by other investigators who used portosystemic shunts as emergency treatment or to prevent bleeding [26-39]. We believe that

several factors were responsible for the consistent results of EPCS that we have obtained over a period of four decades. We reviewed these factors in a recent publication [15]. Briefly, they are: (1) simplification of the diagnostic workup by elimination of unnecessary studies as a routine prior to definitive therapy, which made it possible to accomplish the entire diagnostic workup at the bedside in less than 8 hr without moving the patients out of the ICU, (2) adoption of a specific protocol for an organized system of care before and after EPCS, something that is difficult to accomplish with uniformity in multi-institutional studies. Patients in all four arms of our RCTs were admitted directly to the same ICU where the personnel had specific training and long experience in the care of patients with cirrhosis of the liver, and they were returned to that same ICU postoperatively. Care of all patients in all four arms of the RCTs was supervised by one group of attending physicians throughout the study, (3) rigorous, lifelong program of follow-up in which there was an intensification of efforts to obtain dietary protein control and abstinence from alcohol. Visits to the portal hypertension clinic were scheduled monthly for the first postoperative year and every 3 months thereafter. A dietitian who was employed by the RCT grant and was trained in the care of post-shunt, post-EEST, and post-TIPS patients with cirrhosis was stationed in the clinic to counsel the patient at each visit on the restriction of dietary protein intake to 60 g/days. Serious efforts were made to enroll all patients who were alcoholics in an alcohol rehabilitation program, such as Alcoholics Anonymous, or a similar program at our own institution. Our patients with portacaval shunts proved to be more receptive to rehabilitation therapy than many alcoholics perhaps because of their almost lethal experience with massive bleeding and EPCS. The frequency of permanent abstinence, as a result, was 85% in the EPCS group, (4) a low incidence of early and long-term shunt thrombosis. The PCS remained permanently patent in 97.4% of the patients, which is consistent with our past and recent experience with direct side-to-side PCS [14]. Shunt occlusion represents a serious technical failure of surgical therapy and is usually followed by recurrent BEV and often death. As we documented in our recent publication, high rates of occlusion of various types of shunts have been reported from centers known for experience in the treatment of portal hypertension [15].

A frequent criticism of portal-systemic shunt is the observation or assumption that control of bleeding is achieved at the cost of a high rate of PSE. There is a widespread belief that long-term EST of BEV is associated with a substantially lower rate of PSE than treatment by portal-systemic shunt [38,39]. The results of our RCTs are contrary to both of these conclusions. On initial contact before entry in the trial, 19% of patients in each group had PSE, most likely from gastrointestinal bleeding. A history of PSE was noted in 18% of the EEST patients and 29% of the EPCS patients. Chronic, recurrent PSE that required treatment and diminished the quality of life developed in 35% of patients treated by EEST and 15% of patients who received EPCS in RCT No. 1, and in 61% of the patients treated by TIPS compared to 21% of those treated by EPCS in RCT No. 2, a significant difference ($p=0.001$). Forty percent of the patients who experienced posttherapy PSE had PSE pretherapy. This relatively low incidence of PSE in patients with PCS is consistent with our past experience [8-14]. Experience with the patients in this study, and the results in our other studies of EPCS [8-14] demonstrate that a low incidence of PSE is possible when, with the help of rigorous follow-up, patients abstain from alcohol and comply with a diet of moderate protein restriction.

One purpose of the two RCTs that involved 365 randomized patients, and the supplementary analysis of the 1300 unrandomized cirrhotic patients who underwent PCS for BEV was to answer several

questions about the role of emergency treatment of BEV in subsequent LT. In so doing, it is important to recognize that to date no RCTs have been reported in which the relationship of BEV to LT has been examined prospectively. Since our RCT involved a comparison of EST and TIPS with EPCS, the first question is: what is the role of endoscopic therapy of BEV in patients who might subsequently need LT? Several experienced workers at liver transplantation centers have proposed that EST or Endoscopic Variceal Ligation (EVL) is the first line of treatment for BEV, and that "there are ample data in the literature to support long-term sclerotherapy as the treatment of first choice for bleeding esophageal varices" [8,9]. The results of our RCT No. 1 contradict this proposal. EST achieved permanent long-term control of bleeding in only 20% of unselected consecutive patients. The 5-year survival rate of patients treated by EST was only 21%, and median survival was less than 3 years, even with rescue PCS. The reasons why LT was not considered in more patients in the EST group are that death from recurrent bleeding in 44% of patients, frequent PSE often due to noncompliance as well as to recurrent bleeding, and social issues such as continued alcoholism, drug abuse and non-USA residence status obviated considerations of LT. The results of TIPS in RCT No. 2 were not much different.

The second question is: how often following an episode of acute BEV in patients with advanced cirrhosis is LT required? The results of our study indicate that LT is seldom required following control of bleeding by PCS. In our two RCTs, only 6% of the patients were referred for LT, only 3% were approved for LT, and only 8 patients (2%) underwent LT. Of our 1300 unrandomized patients with PCS, only 3.8% of the patients were referred for LT, and only 19 patients (1.5%) underwent LT. Furthermore and most important, if recurrent BEV is prevented, as was true in 100% of the PCS patients, both randomized and unrandomized, prolonged survival occurs, equal to or better than survival following LT. 30-days and 5-years survival rates were 87% and 73%, respectively, following EPCS in 105 patients in RCT No. 1, 83% and 67%, respectively, following EPCS in 600 unrandomized patients, and 98% and 71%, respectively, following elective PCS in 700 unrandomized patients. Survival rates following LT during the period 1988 to 2001 in 46,940 patients reported by the United Network for Organ Sharing (UNOS) were 74.5% at 1 year, 67.4% at 3 years, and 62.7% at 5 years [41]. Clearly, the 5-years survival rate following PCS (73%, 67%, and 71%) was higher than that of the UNOS LT survival rate (62.7%). It is noteworthy that close to one-half of the patients in the RCT (46%) were alive 15 years after EPCS.

The third question is: should transplant surgeons avoid portacaval shunts or surgical decompressive procedures that involve the hepatic hilum in potential LT candidates? There are numerous statements in the transplantation literature urging avoidance of PCS and strong recommendations to that effect from some recognized transplantation centers [5,6,42-45]. However, there are no valid, representative data from prospective studies, randomized or unrandomized, that support such a proposal. Our studies indicate that PCS is the most effective treatment of BEV, invariably prevents recurrence of bleeding, and achieves long-term survival so that the vast majority of patients do not require LT.

The fourth question is: do portosystemic shunts and, particularly, portacaval shunt, affect the outcome of LT? Our RCTs in which only 8 of the 365 patients underwent LT do not provide sufficient data to answer this question. However, the survival rate of the 19 unrandomized patients who underwent LT was 89% after 30 days and 53% after 5 years, which was not significantly different from the survival rates for LT reported by UNOS. PCS did not increase the mortality rate or complications of subsequent LT. Added to the data from our study are at

least 10 reports of retrospective studies in the literature that concluded that portosystemic shunts do not affect the results of subsequent LT [5-7,43-51]. That conclusion has not been contradicted by reported studies.

Liver transplantation plays a central role in the treatment of cirrhosis of the liver. Nevertheless, there are a number of limitations on the use of this important therapeutic measure as a cure for cirrhosis [52]. The most important limitation is unavailability of donor livers. In year 2008 there were 17,167 candidates on the waiting list for LT at the beginning of the year and 16,538 on the waiting list at the end of the year (based on OPTN data as of /31/09). 6,319 candidates, or 37%, received LT. 2,456 patients died or deteriorated while awaiting LT. The median waiting time for LT in 2002 was 974 days and, although the wait was shorter in 2005, it was still 321 days [41]. Furthermore, numerous patients referred for LT have been disqualified for various reasons. Of the patients referred for LT evaluation, 46% in the RCTs and 62% in the unrandomized series were turned down for valid reasons including continued alcoholism, drug abuse, and non-USA resident status. Additionally, the costs of LT are substantial. Direct costs of care, as reflected by charges for patients who underwent EPCS in our RCT including costs of lifelong follow-up, averaged a total of \$150,400 or \$39,400 per year. In contrast, the mean cost of LT for cirrhosis in adult patients in 2008, including 180 days of post-transplant care, averaged \$523,400, which is more than 3 times the lifelong average cost of EPCS [41]. Finally, third-party insurance coverage for emergency treatment of BEV such as EPCS has been readily obtainable, while coverage for LT is sometimes difficult to obtain. At one of our institutions, of 182 patients referred for LT from January through July, 2009, 11% were denied LT because of insurance issues.

In conclusion, in these RCTs of emergency treatment of acute BEV in 365 patients with cirrhosis, supplemented by analyses of 1300 unrandomized patients treated by portacaval shunt, prospective data indicate clearly that BEV by itself should not be considered an indication for LT. Moreover, the data show that PCS should be considered a first-line treatment for BEV since it promptly and permanently stopped variceal bleeding, was accomplished with a relatively low (15%) incidence of subsequent PSE, and produced long-term survival rates equal or superior to those produced by LT. Furthermore, PCS did not increase the mortality rate or complications in the small number of patients who ultimately required LT, a finding that was confirmed by at least 10 retrospective studies reported in the literature. The importance of these results is underscored by the severe shortage of donor organs, the much higher cost of LT compared to PCS, and the substantial difficulties in obtaining insurance coverage for LT in some patients in the population that develops BEV due to cirrhosis.

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Conflict of interest

There was no conflict of interest relevant to this article on the part of any of the authors.

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