

Portal-Systemic Encephalopathy in Emergency Treatment of Cirrhosis and Bleeding Esophageal Varices

Marshall J. Orloff

*University of California, San Diego, Medical Center
USA*

1. Introduction

Bleeding esophageal varices (BEV) is a common and highly lethal complication of cirrhosis of the liver (Graham & Smith, 1981; Smith & Graham, 1982; Burroughs et al., 1989; Bornman et al., 1994; Khan et al., 2006; Orloff et al., 1977; Mikkelsen, 1974; Terblanche et al., 1989; & D'Amico et al., 1995) The mortality rate associated with BEV is highest during the period surrounding the episode of acute bleeding. If the varices remain untreated after recovery from a bout of acute bleeding, we (Orloff et al., 1977) and others observed a 95% incidence of recurrent bleeding, and death within 2 to 5 years in 90% to 100% of the patients. Recurrent bleeding has been reported to develop most often within the first few days after the acute bleeding episode (Graham & Smith, 1981; Smith & Graham, 1982). Thus, it is clear that emergency treatment of acute bleeding is of paramount importance in the care of patients with portal hypertension and esophagogastric varices.

Because of the over-riding importance of emergency treatment of variceal bleeding, from 1958 to 2011 we conducted and reported studies of emergency therapy in patients with cirrhosis (Orloff, 1967; Orloff et al., 1980; Orloff et al., 1992); Orloff et al., 1994; Orloff et al., 1995a; Orloff et al., 2009a; Orloff et al., 2009b; Orloff et al., 2011a; Orloff et al., 2011b; Orloff et al., 2010; Orloff et al., 2011c; Orloff et al., 2011d; Orloff et al., 2011e; Orloff et al., 2011f; Orloff et al., 2011g; Orloff et al., 2011h; Orloff et al., 2011i). Our studies have been distinguished by three features that, together, make them different from other reported investigations. All patients admitted to our institution with cirrhosis and BEV ("all comers"), regardless of their condition, were included without selection; the specific emergency treatment undergoing evaluation was administered within 24 hours and usually within 8 hours of initial contact; and our studies were prospective, meaning that a well-defined protocol was consistently used and data were collected on-line. Evaluation, prevention, and treatment of portal-systemic encephalopathy (PSE) were an important part of each of our studies.

2. The Eck fistula

In 1877, Nikolai V. Eck (1849-1908), a 29-year-old military surgeon working in the Military Medical Academy in St. Petersburg, published a brief article describing his experiments and

technique for creating a portacaval shunt (Eck fistula) in eight dogs (Eck, 1877). This was not only the beginning of the surgical treatment of portal hypertension but also the first vascular anastomosis. In his article, Eck stated: "I am conducting these experiments with the purpose of clarifying some physiologic problems as well as to determine whether it would be possible to treat some cases of mechanical ascites by means of forming such a fistula. I operated on 8 dogs, one recovered completely and lived in the laboratory for 2.5 months. Because of lack of attention, he ran away. I had to postpone further experiments because I was called to join the active army."

Eck's work would probably have remained unknown outside Russia had it not been for Ivan Pavlov (1849-1936), who used the procedure extensively in laboratory studies of liver physiology and named the operation the Eck fistula, giving full credit to Eck for its invention (Hahn et al., 1893; Pavlov, 1893). The landmark description by Pavlov et al. of portal-systemic encephalopathy (PSE) following feeding meat to dogs with an Eck fistula, which they called "meat intoxication," was part of the work that resulted in Pavlov's receiving the Nobel Prize in 1904 for his contributions on the physiology of digestion. Pavlov spent his entire career at the Military Medical Academy in St. Petersburg, the same institution where Eck developed the portacaval shunt. Since its original description, the Eck fistula has been used extensively for a wide range of studies in animals and humans and clinically for the treatment of the life-threatening complications of portal hypertension.

3. Portal-Systemic Encephalopathy (PSE)

Hepatic encephalopathy is a neuropsychiatric disorder that results from impaired liver function. It occurs in two distinct forms: (1) in acute or fulminant hepatic failure it takes the form of a neurological disorder that progresses from altered mental status to coma, generally within hours or days, and is associated with increased intracranial pressure caused by massive brain edema; (2) portal-systemic encephalopathy (PSE), which commonly occurs in cirrhosis, in which there are spontaneous or created portal-systemic shunts that permit toxins of intestinal origin to bypass the liver into the systemic circulation. Neurologically, PSE develops slowly, starting with sleep abnormalities, shortened attention span, and muscular incoordination, progressing through lethargy, ataxia, stupor, and coma. PSE is often precipitated by event such as gastrointestinal bleeding, uremia, hypokalemia, or ingestion of excessive amounts of protein. Neuropathologically, PSE is characterized by astrocytic rather than neuronal changes, and brain edema and intracranial hypertension are not found.

Since the description in 1893 of "meat intoxication" in the Eck fistula dog by the Pavlov group, animals with a portacaval shunt (PCS) (Eck fistula) have been used extensively for research studies of the pathogenesis and treatment of PSE (Hahn et al., 1893). The PCS rat has been consistently reported to have neurobehavioral abnormalities when subjected to sophisticated testing (Bengtsson et al., 1980; Tricklebank et al., 1978). One of the best animal models of chronic recurrent PSE is the dog with a congenital or surgically created PCS (Maddison et al., 1991). Animal and human studies have demonstrated that chronic liver failure and spontaneous or created PCS result in the accumulation of neurotoxic substances in the brain. Two such substances are ammonia and manganese.

Ammonia derived from colonic bacteria as well as from the deamination of glutamine in the small bowel is absorbed by passive diffusion and normally undergoes a high first-pass

extraction by the liver (Cordoba & Blei, 1997). In chronic liver failure, hepatic urea synthesis declines and this, in addition to portal-systemic shunting, results in increased blood ammonia concentrations. Furthermore, cirrhotic patients are hypersensitive to ammoniagenic conditions such as an oral protein load or gastrointestinal hemorrhage. An illustration of this hypersensitivity is provided by a report of studies in the 1950s in which attempts were made to treat ascites in cirrhotic patients with ion-exchange resins that absorbed sodium but released ammonium ions (Gabuzda et al., 1952). This treatment led to a significant reduction in ascitic volume but precipitated severe PSE in many of the patients treated. If present in high concentrations, ammonia has the potential to adversely affect central nervous system (CNS) function by several mechanisms, which include a direct effect of the ammonium ion on inhibitory and excitatory neurotransmission as well as inhibition of the tricarboxylic acid cycle enzyme ketoglutarate dehydrogenase, with potential impairment of brain energy metabolism (Szerb & Butterworth, 1992; Lai & Cooper, 1986). However, brain energy metabolism does not appear to be impaired in chronic liver failure until very late stages associated with isoelectric electroencephalography (EEG) traces (Hindfelt et al., 1977). On the other hand, increases of cerebrospinal fluid lactate have been described both in cirrhotic patients with PSE (Yao et al., 1987) and in experimental animals with chronic liver failure and ammonia-precipitated encephalopathy (Therrien et al., 1991), findings that are consistent with an inhibitory effect of ammonia on cerebral glucose oxidation.

Other effects of ammonia on cerebral function include a stimulatory effect on L-arginine uptake by brain preparations resulting in increased production of nitric oxide (Raghavendra Rao et al., 1995) and inhibition of the capacity of astrocytes to accumulate glutamate (Bender & Norenberg, 1996; Knecht et al., 1997) a major excitatory neurotransmitter.

In 1963, we performed a study that subsequently influenced the use of PCS in the treatment of portal hypertension and variceal hemorrhage. We examined the influence of the stomal size of the portacaval anastomosis, and in turn of the blood flow rate through the anastomosis, on peripheral blood ammonia levels (Orloff et al., 1963). Induced ammoniemia was studied in two groups of dogs, one of which had large end-to-side PCS measuring at autopsy 2.0-4.2 cm in greatest diameter, and the other of which had small end-to-side PCS measuring 0.5-1.8 cm in greatest diameter. A third group of intact dogs served as controls. Ammoniemia was induced by three standardized methods that consisted of the administration by gavage of ammonium citrate (0.5 g/kg), gavage of fresh whole blood (30 mL/kg) plus urease (4 U/mL), and gavage of fresh whole blood (30 mL/kg) alone. All three techniques of ammonium loading resulted in significantly higher mean peak blood ammonia levels in the dogs with large shunts than in those with small shunts. Furthermore, in the animals with large shunts, markedly elevated blood ammonia concentrations persisted for longer periods of time. Measurements of the pressure gradients across the shunts at operation revealed a mean gradient of 31.0 mm saline in the small-shunt group as compared to only 3.0 mm in the large-shunt group. A consistent inverse relationship was demonstrated between the height of the blood ammonia level and the magnitude of the pressure gradient across the portacaval anastomosis. Application of Gorlins' hydraulic formula to these studies provided support for the presumption that the magnitude of ammoniemia was directly related to the blood flow rate through the shunt. We concluded that the stomal size of end-to-side PCS, and in turn the rate of blood flow through the shunts, have a definite influence on the concentration of ammonia in the peripheral blood of

the dog. These results suggested the possibility of a relationship between shunt size and postshunt PSE. The results of this study served as the basis for the subsequent use of reduced-caliber PCS in the treatment of variceal bleeding (Sarfeh & Rypins, 1994; Zervox et al., 1998).

In addition to ammonia, chronic liver failure and portal-systemic shunting result in increased blood and brain concentrations of manganese (López-Novoa, 1988; Fitzhugh & Nelson, 1948; Dashti et al., 1989; & Nuber et al., 1980). Manganese is neurotoxic, affecting both neuronal and astrocytic integrity. In the case of astrocytes, exposure to manganese results in altered expression of several key astrocytic proteins (Hazell et al., 1999a; Hazell et al., 1999b) and Alzheimer type II changes (Weissenborn et al., 1995).

Other toxins in addition to ammonia and manganese are known to increase in the systemic circulation in chronic liver failure. Such toxins include mercaptans, phenols, and short-chain fatty acids (Zieve et al., 1974). While there is no convincing evidence that these toxins alone cause cerebral dysfunction in chronic liver failure, they could combine with ammonia or manganese to act synergistically (Zieve, 1989).

Recently, attention has been focused on changes in brain neurotransmitter systems as the likely mediators of the neuropsychiatric manifestations of PSE in chronic liver failure. Recent studies using molecular biological approaches continue to confirm that, when liver fails, brain responds with significant alterations in gene expression. In many cases, these alterations involve genes that code for neurotransmitter-related proteins, many of which are essential for CNS function. Many of the symptoms of early PSE in chronic liver failure, such as altered personality, depression, and inverted sleep patterns, are symptoms that have classically been associated with alterations in biogenic amine function. FNA extracts of brain tissue obtained at autopsy from cirrhotic patients who died in hepatic coma have been found to show increased expression of the neuronal isoform of the monoamine-metabolizing enzyme MAO-A (Mousseau et al., 1997). This increase in MAO-A gene expression was found to be associated with increased activities of the enzyme and increased densities of catalytic sites on the enzyme protein (Mousseau et al., 1997). Moreover, studies of the same brain extracts revealed increased concentrations of homovanillic and -hydroxyindoleacetic acids, the final metabolites of dopamine and serotonin, respectively (Bergeron et al., 1989). Increased concentrations of 5-hydroxyindoleacetic acid were also reported in cerebrospinal fluid from patients (Young & Lai, 1980) and experimental animals (Bergeron et al., 1995) with chronic liver failure. On the basis of these findings, it has been suggested that altered monoaminergic function may be responsible for the early neuropsychiatric symptoms of PSE in chronic liver disease (Bergeron et al., 1995; Bergeron et al., 1990).

The “*peripheral-type*” benzodiazepine receptor (PTBR) is a heterooligomeric protein complex located (like MAO-A) on the outer mitochondrial membrane of the astrocyte. Increased PTBR gene expression has been reported in brain extracts from rats with PCS (Desjardins et al., 1997). This increased gene expression resulted in increased receptor sites in the brains and peripheral tissues of these animals as revealed by quantitative receptor autoradiography and the high selective PTBR ligant [³H] PK 11195 (Giguère et al., 1992; Raghavendra Rao et al., 1994). Increased [³H] PK 11195 binding sites were also reported in autopsied brain tissue from cirrhotic patients who died in hepatic coma (Lavoie et al., 1990).

There is evidence to suggest that the increased expression of PTBRs in brain in chronic liver failure is the consequence of exposure to ammonia and/or manganese. The precise mechanism whereby increased expression or activation of PRBRs results in altered brain excitability characteristic of PSE has not been established. PCS in the rat results in increased gene expression of the constitutive (neuronal) isoform of nitric oxide synthase (nNOS) in brain (Raghavendra Rao et al., 1997a). Increased nNOS mRNA is accompanied by increased nNOS protein (Raghavendra Rao et al., 1997a) and by increased nNOS enzyme activities. Recent evidence suggests that, in addition to an induction in nNOS gene expression, increased nNOS activities may also result from a stimulatory effect of ammonia on L-arginine uptake by neuronal preparations shown both *in vitro* and *in vivo* (Raghavendra Rao et al., 1997b). Increased production of NO as a consequence of increased nNOS activities could contribute to the alterations of cerebral perfusion observed in chronic liver disease (Raghavendra Rao et al., 1998).

The appearance of extrapyramidal symptoms, particularly rigidity, in cirrhotic patients with end-stage liver disease has prompted, by analogy with the well-established dopamine deficit in Parkinson's disease, evaluations of the dopamine system in relation to PSE. Studies in autopsied brain tissue from cirrhotic patients (Bergeron et al., 1989) and from rats with PCS (Bergeron et al., 1995) reveal several-fold increases in concentration of the dopamine metabolite homovanillic acid, a finding that could result from increased activities of monoamine oxidase reported in the same material (Mousseau et al., 1997). In another study, densities of the postsynaptic dopamine D₂ receptor were significantly reduced in pallidum/putamen from cirrhotic patients (Mousseau et al., 1993) a finding that could have resulted from manganese deposition in the brains of these patients (Pomier Layrargues et al., 1995).

Strategies aimed at the prevention and treatment of PSE in chronic liver failure are of two major types, namely, ammonia-lowering strategies and approaches aimed directly at the CNS (Cordoba & Blei, 1997; Ferenci et al., 1996). Since PSE is frequently precipitated by ammoniagenic situations such as an oral protein load or a gastrointestinal hemorrhage, various treatment modalities are aimed at the gut. Such strategies include reduction of the absorption of nitrogenous substances arising from bacterial action in the colon. Colonic cleansing reduces the luminal ammonia content and lowers blood ammonia content in cirrhotic patients (Wolpert et al., 1970). Nonabsorbable disaccharides are routinely used to decrease ammonia production in the gut. The action of the most popular substance in this class, lactulose, involves increased fecal nitrogen excretion by facilitation of the incorporation of ammonia into bacteria as well as a cathartic effect (Cordoba & Blei, 1997). Lactulose administered orally reaches the cecum, where it is metabolized by enteric bacteria, causing a fall in pH (Brown et al., 1974). The dose is adjusted to produce two or three soft bowel movements daily (Cordoba & Blei, 1997).

Antibiotics such as neomycin are also useful for lowering blood ammonia, mainly by an effect on ammonia production by intestinal bacteria. However, neomycin therapy may be associated with some toxic side effects (Cordoba & Blei, 1997). More recently, rifaximin, a nonabsorbable derivative of the antibiotic rifamycin, has been shown to be effective in lowering blood ammonia and has proven to be of superior efficacy compared with lactulose (Bismuth et al., 2011; Munoz, 2008). Most of an orally administered dose is eliminated unchanged in the feces. Thus, it lacks significant toxicity and side effects because of minimal gastrointestinal absorption.

Restriction of dietary protein remains a cornerstone of therapy for PSE in cirrhotic patients and has been an essential part of our treatment of patients with bleeding esophageal varices following portacaval shunt (Wolpert et al., 1970). However, long-term nitrogen restriction is potentially harmful and a positive nitrogen balance is necessary to promote liver regeneration as well as to increase the capacity of skeletal muscle to remove ammonia in the form of glutamine (Lockwood et al., 1979). Protein intake of 1 g/kg per day may be required in order to maintain an adequate nitrogen balance (Swart et al., 1989).

An alternative strategy for the lowering of blood ammonia is the stimulation of ammonia fixation (Desjardins et al., 1997). Under normal physiological conditions, ammonia is removed by the formation of urea in periportal hepatocytes and by glutamine synthesis in perivenous hepatocytes, skeletal muscle, and brain. In cirrhosis, both urea cycle enzymes and glutamine synthetase in liver are decreased in activity. Strategies to stimulate residual urea cycle activities and/or glutamine synthesis have been tried over the past 20 years. One of the most successful agents to be used so far is L-ornithine-L-aspartate (OA). RCTs with OA demonstrate significant ammonia lowering and concomitant improvement in psychometric test scores in cirrhotic patients with PSE (Kircheis et al., 1997). Studies in experimental animals suggest that the metabolic basis for the beneficial effect of OA on blood ammonia in chronic liver failure resides in its ability to stimulate residual hepatic urea cycle function and also to promote glutamine synthesis, particularly in skeletal muscle (Rose et al., 1998).

Benzoate is also effective in reducing blood ammonia both in patients with inherited urea cycle disorders and in cirrhotic patients [64]. In a RCT with sodium benzoate versus lactulose, improvement in neuropsychiatric performance was found to be comparable using both treatments (Sushma et al., 1992).

In contrast to the multiple strategies used successfully to lower blood ammonia and improve neurological status in patients with chronic liver failure, drugs that act directly on neuronal excitability have not been widely applied in this patient group. The major reason for this is that the precise neurotransmitter changes responsible for PSE in chronic liver failure are still being elucidated. Some attempts to treat PSE in cirrhotic patients with benzodiazepine receptor antagonists and dopamine agonists have occurred, but with limited success.

Several RCTs have been performed to assess the efficacy of the benzodiazepine receptor antagonist flumazenil in cirrhotic patients with various degrees of severity of PSE [69]. Spectacular improvements in neuropsychiatric status were recorded in a subset of patients receiving flumazenil (Pomier Layrargues, 1994; Gyr et al., 1996). However, enthusiasm for this approach has been tempered by the possible confounding effects of prior exposure to benzodiazepines and the seeming lack of correlation between clinical response and blood levels of substances with benzodiazepine receptor agonist properties in these patients (Butterworth et al., 1995).

4. Emergency portacaval shunt for bleeding esophageal varices

Portal-systemic shunt is the only available definitive treatment for portal hypertension-related bleeding. Numerous studies have shown that a technically satisfactory PSS will permanently solve the problem of bleeding in the vast majority of patients. The obvious

potential advantage of performing this procedure under emergency circumstances is that, unlike other forms of treatment, it can be expected to provide both immediate and prolonged control of hemorrhage. The question is, can cirrhotic patients tolerate an operation of this magnitude when it is performed as an emergency in the face of bleeding? To answer this question, we have conducted *prospective* studies of emergency PCS (EPCS) over the past 47 years, as follows: (1) an unrandomized study of 400 unselected patients who underwent EPCS; (2) a RCT of EPCS versus emergency medical therapy involving 43 patients at our Veterans Administration Hospital; (3) an unrandomized study of 94 unselected, consecutive patients with Child's class C cirrhosis; (4) a RCT of portacaval shunt versus endoscopic sclerotherapy in 518 unselected patients bleeding from gastric varices; (5) an unrandomized study in 12 patients with uncontrollable bleeding from portal hypertensive gastropathy; (6) a NIH grant supported RCT of EPCS versus emergency endoscopic sclerotherapy (EST) that enrolled 211 patients who have had more than 10 years of follow-up or until death; and (7) a NIH grant supported RCT of TIPS versus EPCS that enrolled 154 patients who have been followed up for 5-10 years (Orloff, 1967; Orloff et al., 1980; Orloff et al., 1992; Orloff et al., 1994; Orloff et al., 1995a; Orloff et al., 2009a; Orloff et al., 2009b; Orloff et al., 2011a; Orloff et al., 2011b; Orloff et al., 2010; Orloff et al., 2011c; Orloff et al., 2011d; Orloff et al., 2011e; Orloff et al., 2011f; Orloff et al., 2011g; Orloff et al., 2011h; Orloff et al., 2011i; Orloff & Bell, 1983; Bell, et al., 1981; Orloff, 1968; Orloff, 1969; Orloff et al., 1974; Orloff et al., 1975; Orloff & Bell, 1986; Orloff et al., 1995b; Orloff et al., 1997) . The unique features of our studies that, together, make them different from other reported investigations are as follows: (1) EPCS was undertaken within 24 h of initial contact of the patient with our institution in one study and within 8 h in the other six studies; (2) the patients were unselected, which means that all patients with bleeding varices, regardless of their condition ("all comers"), 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-year follow-up rates were 100, 98, and 97%, respectively. A total of 1,432 patients have been involved in these studies.

5. Portal-systemic encephalopathy in our RCT of endoscopic sclerotherapy versus emergency portal shunt

5.1 Quantitation of PSE

This recently published RCT is representative of all of our studies (Orloff et al., 2009a; Orloff et al., 2009b). PSE was quantitated during hospitalizations and at each clinic visit by grading 4 variously weighted components on a scale of 0 to 4: (1) mental state, (2) asterixis, (3) number connection test, and (4) arterial blood ammonia. A PSE Index was calculated according to the method of Conn et al. (Conn & Lieberthal, 1978) in which the scores of the 4 components were added to yield a PSE Sum, and then divided by the maximum possible PSE Sum. Mental state was given a weight of 3 and the other components a weight of 1. To increase objectivity, a senior faculty gastroenterologist who was not otherwise involved in the BEV study evaluated each patient for PSE during the clinic visits. The gastroenterologist was "blinded" in that he was not told what therapy the patient had received.

The definition of PSE was based on any one of the following criteria: (1) classical signs of altered mental status on physical examination performed by an experienced faculty physician; (2) classical signs of altered mental status described by outside physicians, close relatives of the patient, or the patient himself; (3) a high PSE Index of 0.33 or greater. Electroencephalography was not included in the evaluation because it was considered cumbersome, costly, and impractical given the numerous programmed and unprogrammed outpatient clinic and emergency department visits made by the patients. Patients were classified as having recurrent PSE when they had 2 or more episodes of PSE after primary therapy.

5.2 Incidence of PSE

Patients who were discharged from the hospital and survived more than 30 days after entry in the study numbered 93 in the EST group and 89 in the EPCS group. Calculations of the incidence and manifestations of recurrent PSE are based on this population. Deaths on or before 30 days were considered indeterminate and were unrelated to PSE. Dietary protein tolerance up to 80 g per day was observed in all patients before discharge. A 60-g protein restriction was prescribed upon discharge. Table 1 and Fig. 1 show data on this group of patients. Patients who developed recurrent PSE after discharge from the initial hospital admission numbered 33 or 35% in the EST group and 13 or 15% in the EPCS group. The difference was highly significant with a P value of 0.001.

	EST (n = 93)	EPCS (n = 89)	p Value
Incidence of recurrent PSE - n (%)	33 (35)	13 (15)	0.001*
Incidence of transient PSE - n (%)	3 (3)	3 (3)	1.0
Length of survival:			
Total days	133,243	266,169	<0.001*
Total years	364.8	728.7	
Total days per patient	1432.7	2990.7	
Total years per patient	3.9	8.2	
Episodes of recurrent PSE			
Total episodes - n (n/person)	179 (1.92)	94 (1.06)	0.003*
Episodes per year of follow-up	0.49	0.13	
Interval between episodes (years)	2.03	7.74	
Hospital readmissions for recurrent PSE			
Total readmissions - n (n/person)	146 (1.57)	87 (0.98)	0.003*
Readmissions per year of follow-up	0.40	0.12	
Interval between readmissions (years)	2.50	8.38	
Cause of recurrent PSE episodes - n (%)			<0.001*
Dietary protein indiscretion	75 (42)	60 (64)	
UGI bleeding	57 (32)	8 (9)	
Infection	18 (10)	12 (13)	
Alcoholism	28 (16)	4 (4)	
Uncontrolled diabetes	2 (1)	11 (12)	
Hepatic failure	5 (3)	0 (0)	
Other	7 (4)	5 (5)	

Timing of first episode of recurrent PSE - n (%)			0.30
First 6 months	17 (52)	8 (62)	
Second 6 months	6 (18)	1 (8)	
Year-1	23 (70)	9 (69)	
Year-2	4 (12)	3 (23)	
Year-3	2 (6)	0 (0)	
Year-4	0 (0)	0 (0)	
Year-5	1 (3)	0 (0)	
Year >5	3 (9)	1 (8)	
Timing of all episodes of recurrent PSE - n (%)			0.33
First 6 months	24 (15)	23 (24)	
Second 6 months	31 (19)	8 (8)	
Year-1	55 (34)	31 (33)	
Year-2	46 (28)	32 (34)	
Year-3	18 (11)	11 (12)	
Year-4	15 (9)	14 (15)	
Year-5	4 (2)	1 (1)	
Year >5	26 (16)	6 (6)	
Relationship of recurrent PSE to survival - Years (median, 95% CI)			
Patient with recurrent PSE:			
Overall survival	2.90 (1.5, 4.74)	5.18 (1.26, Inf)	
Survival after first PSE	1.23 (0.94, 3.17)	4.14 (1.17, Inf)	
Patients free of recurrent PSE:			
Overall survival	3.26 (2.00, 4.34)	10.37 (6.19, Inf)	
P value - Recurrent PSE vs. no PSE	0.042*	0.001*	
High PSE Index - n (%)			
Patients with PSE Index ≥ 0.33	19 (20)	12 (13)	0.24
Patients with PSE Index ≥ 0.33 who had recurrent clinical PSE	15 (79)	4 (33)	0.022*

* statistically significant difference

Table 1. Recurrent PSE in Patients Who Survived >30 Days and Were Discharged from the Hospital

The 93 early survivors in the EST group lived for a collective total of 364.8 years, while the 89 early survivors who underwent EPCS lived a collective total of 728.7 years, twice as long as the EST patients ($p < 0.001$). The patients with recurrent PSE in the EST group had a collective total of 179 episodes of PSE and were readmitted to the hospital 146 times for treatment of PSE. In contrast, the patients with recurrent PSE following EPCS, experienced 94 episodes and 87 hospital readmissions. The calculated yearly frequency of PSE episodes was 0.49/yr in the EST group and 0.13/yr in the EPCS group, and the calculated hospital readmission rate was 0.40/yr in the EST patients and only 0.12/yr in the EPCS patients ($p = 0.003$). Expressed as per-patient average, patients in the EST group were hospitalized for recurrent PSE every 2.50 years, while patients who were treated by EPCS required hospitalization for recurrent PSE every 8.38 years ($p = 0.003$).

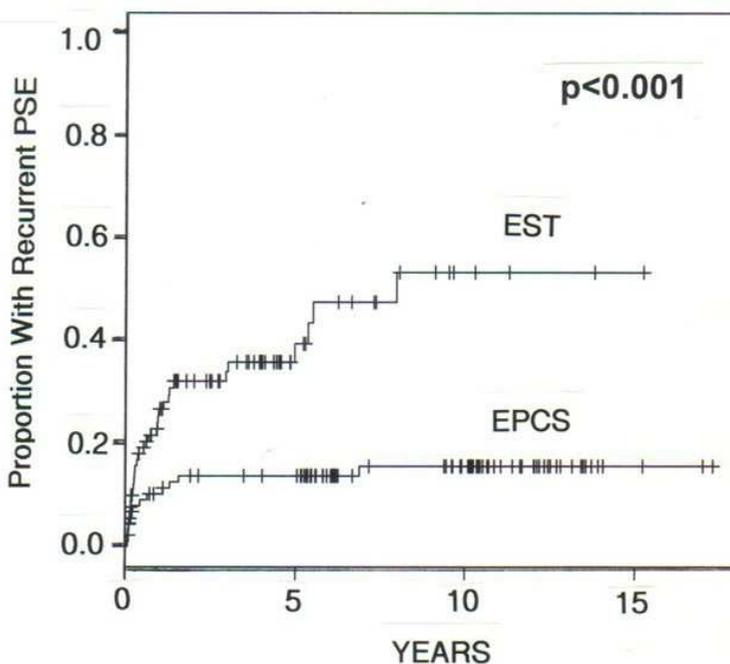


Fig. 1. Incidence and timing of recurrent PSE in patients who were randomized to EST (n=93) or EPCS (n=89) and survived >30 days and were discharged from the hospital.

5.3 Cause of recurrent PSE

Dietary indiscretion with regard to protein restriction was the most frequent cause of recurrent PSE in both groups more so in the patients treated by EPCS. Portal hypertension-related UGI bleeding, usually from esophageal varices, was the main cause of recurrent PSE in 32% of the episodes experienced in patients treated by EST, and was a contributing cause in an additional 18%. Gastrointestinal bleeding was infrequently responsible for PSE in patients who underwent EPCS ($p < 0.001$). Thus, gastrointestinal bleeding played a role in 57 episodes of PSE in the EST group, compared to 8 episodes in the EPCS group, and undoubtedly was a major factor in the higher incidence of recurrent PSE following EST. Other conditions responsible for at least 10% of PSE episodes were infection, alcoholism, and uncontrolled diabetes.

5.4 Relationship of recurrent PSE to survival

In the EST group, patients with recurrent PSE lived a median 2.90 years while those who remained free of PSE lived a median 3.6 years, a longer period of time. This difference was significant ($p = 0.042$) with a hazard ratio of death due to recurrent PSE of 1.60 (95% confidence interval 1.01, 2.56). It is not possible in the EST group to determine the effect of PSE on survival because of other factors, particularly recurrent BEV, which influenced survival.

In the EPCS group, patients who remained free of PSE lived a median 10.37 years, significantly longer than those with recurrent PSE who survived a median 5.18 years. The difference was significant ($p=0.001$). It is tempting to attribute the longer survival to freedom from PSE, but the many factors that affect survival make it inappropriate to single out PSE as the main determinant of life or death.

The results with regard to PSE of our randomized controlled trial are contrary to conventional beliefs about both portacaval shunt and endoscopic sclerotherapy. The incidence of recurrent PSE during long-term follow-up of unselected patients treated by EPCS was only 15%, which was significantly lower than the 35% incidence of PSE following emergency and long-term EST. Moreover, every aspect of PSE was less severe following EPCS than after EST. The number of PSE episodes was fewer (94 vs. 179), the number of hospital readmissions for PSE was fewer (87 vs. 146), the calculated yearly frequency of PSE was lower, and the calculated per-patient average hospitalization for PSE was less frequent (once every 8.38 yr vs. once every 2.50 yr) in the EPCS group than in the EST patients.

A number of factors appear to have played a role in causing PSE, but two of these factors were predominant. The first was dietary protein indiscretion. Despite concerted, repeated and often successful efforts to educate patients on limiting dietary protein intake to 60 g per day, dietary protein indiscretion was responsible for 75 of the 179 episodes of PSE in the EST group and 60 of the 94 episodes of PSE in the EPCS group. The second causative factor was recurrent variceal bleeding which was directly responsible for 32% of the episodes of PSE in patients treated by EST, and was a major contributing cause in an additional 18% of the episodes. In contrast, UGI bleeding at best may have been responsible for only 8 of the 94 episodes of PSE in patients who had EPCS. It appears highly likely that the higher incidence of PSE following EST compared to EPCS was due to the failure of EST to achieve long-term control of BEV. It is noteworthy that resumption of alcoholism may have played a role in only 12% of the episodes of PSE. These results demonstrate that a low incidence of PSE is possible when patients are free of recurrent UGI bleeding, abstain from alcohol, and comply with a diet of moderate protein restriction.

6. Portal-systemic encephalopathy in our RCT of TIPS versus emergency portacaval shunt

We have completed a RCT of emergency TIPS versus EPCS that enrolled 154 unselected consecutive patients who have been followed up for 5 to 10 years. The results of this RCT have been submitted for publication (Orloff et al., 2011h; Orloff et al., 2011j). Transjugular intrahepatic portosystemic shunt, or TIPS, is a side-to-side portacaval shunt performed radiologically by a percutaneous approach. It is the most widely used form of portal decompression and is used to control BEV when other measures, such as endoscopic treatment and pharmacologic therapy, have failed. The major shortcomings of TIPS reported in numerous studies have been a high incidence of occlusion of the shunt and the frequent occurrence of PSE.

In our RCT, regular follow-up to determine patency of the TIPS and EPCS revealed stenosis or occlusion of the TIPS in 84% of this group of patients. Patients treated by TIPS had a mean 2.1 episodes of TIPS stenosis or occlusion. Revision of the TIPS by balloon angioplasty or insertion of one or more additional stents was performed in 63% of the patients with TIPS

malfunction. The revisions failed in 80% of the patients. The consequences of TIPS malfunction were recurrent BEV and PSE. Durability of TIPS was disappointing. In marked contrast, EPCS remained permanently patent in 97% of the patients in that groups, as a result of which there was permanent prevention of recurrent BEV and a significantly lower incidence of PSE. In the overall, 61% of the patients treated by TIPS developed recurrent PSE, compared to 21% of the patients treated by EPCS. The three-fold greater incidence of recurrent PSE in the TIPS group was highly significant ($p < 0.001$).

In both of our recently reported RCTs, EPCS was a total shunt that involved a direct anastomosis between the portal vein and inferior vena cava. EPCS permanently controlled variceal bleeding, resulted in long-term survival that was substantially greater than that obtained by EST, and was followed by a relatively low rate of PSE that was less than one-half the rate associated with EST. How do we account for the low incidence of PSE? We believe that a number of factors played an important role in the results achieved by EPCS in our study. First, and most important, EPCS was uniformly successful in preventing recurrent BEV, a frequent cause of PSE. Second, hepatic function improved and stabilized in a substantial majority of patients as a result of both freedom from bleeding and abstinence from alcohol, which was permanent in 62% of the patients. Third, follow-up evaluation and support was rigorous, frequent and lifelong in all patients. Fourth, follow-up included regular counseling by a dietitian on restriction of dietary protein intake to 60 g/day, an amount that is quite ample for nutrition and is compatible with an appetizing diet. A high level of patient compliance was obtained by repeated education about the importance of moderate protein restriction. Fifth, long-term patency and function of the portacaval shunt was obtained in 98% of patients. No one of these factors alone can account for the low incidence of PSE, but together they resulted in a rate of PSE that was less than one-half the rate associated with EST.

7. Conclusions

In these prospective randomized controlled trials of emergency treatment of acute bleeding esophageal or gastric varices in 4 separate studies involving 628 unselected, consecutive patients with cirrhosis of all grades of severity, EPCS was followed by a 15-21% incidence of recurrent PSE, which was significantly lower than the 35% incidence of PSE that followed emergency and long-term EST and the 61% incidence associated with TIPS. These results contradict the widespread belief that portal-systemic shunts are associated with a high incidence of PSE. Moreover, these results call into question the widespread practice of using portal-systemic shunt mainly or only as salvage for failure of endoscopic and pharmacologic therapy because of the belief that the superior control of variceal bleeding by surgery is offset by life-threatening PSE.

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Phone: +385 (51) 770 447
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Phone: +86-21-62489820
Fax: +86-21-62489821

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