Is surgical portosystemic shunt the treatment of choice in Budd-Chiari Syndrome ?

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Introduction

Budd-Chiari syndrome (BCS) consists of hepatic venous outflow obstruction and its manifestations, regardless of the cause and regardless of the level of obstruction from the small hepatic veins to the entrance of the right atrium (1). Outflow obstruction caused by hepatic veno-occlusive disease and cardiac disorders are excluded. Although the cause, the mechanism and the nature of the obstacle are not given, the term Budd-Chiari Syndrome should be retained according to the European Group for the Study of Budd-Chiari Syndrome (The Prague nomenclature for BCS) (1).

Clinical presentation is variable depending on the degree and the speed of venous obstructions (2). Its presenting symptoms vary widely from mild ascites with slightly elevated liver function easily controlled by diuretics and anticoagulants, to acute liver failure requiring liver transplantation.

BCS is considered asymptomatic when there is neither abdominal pain, ascites nor hepatomegaly, jaundice, leg oedema, encephalopathy or gastro-intestinal bleeding nor any history of them.

Based partly on our personal experience (3), manifestations and duration of BCS should permit to classify BCS according to "Prague Classification" in asymptomatic, acute, subacute, chronic or acute-on-chronic forms (table 1) (1). BCS is caused by a wide variety of causes either secondary to obstruction originating from extravenous lesion (tumor, abscess, cysts) or primary from endoluminal venous lesion (thrombosis, webs, endophlebitis). The cause of secondary BCS can be identified by sonography, computed tomography, or magnetic resonance imaging, completed by serologing testing and liver biopsy as appropriate. Primary BCS is associated in our experience with one or several underlying thrombogenic conditions (mainly myeloproliferative disorders) in more than 80% of the cases (3,4) making ignorance of cause of BCS rare.

The prognosis of BCS is dependent on the severity of symptoms of BCS (we have recently shown the usefulness of the Child-Pugh score and clinico-pathological classification of BCS) (3,7) and the severity of the underlying disease Natural history of Budd-Chiari syndrome has long been considered as progressive and almost uniformly fatal (5,6). However, it was recently shown that the outcome has improved in recent years, likely as a result of better recognition and treatment (3,7, 8).

Treatments of Budd-Chiari syndrome

There are numerous therapeutic modalities of BCS including medical treatments (diuretic therapy, anticoagulant therapy and thrombolysis), radiological treatments (angioplasty with expandable venous stents) (9) and surgical treatments (portosystemic shunt, liver transplantation).

Medical treatment, including therapy of the frequent underlying haematological disease, anticoagulation, and diuretics may successfully control the disease especially if the ascites is easily treated without deterioration of the liver function. Patients who do not improve or develop severe complications of portal hypertension such as refractory ascites, spontaneous bacterial peritonitis, oesophageal variceal bleeding or progressive liver failure, despite medical treatment are in general considered for derivative treatment or liver transplantation.

Orthotopic liver transplantation (OLT) has been considered for the last years, as the treatment of choice in patients with BCS and hepatic failure (10). More recently liver transplantation has also been proposed in patients with earlier disease stages (11) because of good long term results and the possibility to definitively treat several prothrombotic states such as protein C, protein S and antithrombin III deficiencies. With respect to a limited number of reports of OLT for BCS found in the literature, it seems currently admitted that OLT should be considered as an effective treatment for fulminant or chronic progressive BCS with failure of conventional treatment. However, mortality and morbidity after OLT seemed higher than expected in young patients possibly related to technical difficulties (adhesions, portal hypertension, large liver size) and wasting of the patients.

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Table 1. — **Prague Classification for Budd-Chiari Syndrome**

Aetiology	Site of obstruction	Manifestations and duration of disease*	
Primary : Obstruction originating from endoluminal lesion (thrombosis, webs, endophlebitis)	Small hepatic veins Large hepatic veins Hepatic vein ostia Inferior vena cava Combined sites of obstruction	Asymptomatic	No ascites, hepatomegaly, abdominal pain, jaundice, oedema, encephalopathy and gastro-intestinal bleeding
		Acute**	Duration of symptoms less than 1 month (usually rapid development of ascites and ALT > 5 times ULN)
		Subacute**	Duration of symptoms 1-6 months
Secondary : Obstruction originating from extravenous lesion (tumor, abscess, cysts)		Chronic	Duration of symptoms more than 6 months and/or biopsy proven cirrhosis (usually gradual development of ascites and ALT < 5 times ULN)
		Acute-on-chronic**	Duration of symptoms more than 6 months and/or biopsy proven cirrhosis. Rapid increase of ascites and ALT > 5 times ULN

***** If the period of symptoms is unknown as undetermined duration of disease.
** Fulminant disease : ALT > 5 times ULN and hepatic encephalopathy grade 3 or 4 ALT alanine aminotransferase ; ULT : upper limit of normal.

Why treat with portosystemic shunt ?

In spite of these therapeutic progresses, surgical portosystemic shunt remains considered as the first-line treatment in patients with BCS to ensure effective liver decompression (12-18,20,22,32).

The bases of this consideration are both experimental and rational.

In the dog, an obstruction of the suprahepatic vena cava causes a Budd-Chiari syndrome with congestive hepatomegaly and ascites disappearing with a side-to-side portocaval shunt (21). This experimental data suggests that BCS manifestations can be explained by following physiopathological mechanisms. The increase of sinusoidal pressure caused by the venous outflow obstruction leads to sinusoidal congestion with hepatomegaly and hepatic pain, portal hypertension and ascites. The mechanism of the development of hepatic failure is described as due to the continuous elevated intrahepatic sinusoidal pressure. In the absence of venous outflow, portal pressure and hepatic arterial pressure lead to an unphysiologic high pressure in the hepatic sinusoids leading to perisinusoidal necrosis of hepatocytes in Rappaport zone 3 eventually leading to liver failure.

These physiological mechanisms explain the excellent control of ascites persisting to medical management in patients with BCS treated with surgical portosystemic shunt (21-22,32). The goal of all therapy in BCS has been to improve hepatic venous outflow. The rationale for portosystemic shunts is to convert the portal vein into an outflow tract for the liver, and this is why end-to-side portocaval shunt is not useful. There is controversy to which shunt, the side-to-side portocaval shunt or the meso-caval shunt is better. Meso-caval shunt was introduced because of the difficulty of performing a side-to-side portocaval shunt in the presence of a hypertrophied caudate lobe (6). The complete obstruction of the inferior vena cava by the caudate lobe precludes the use of the conventional side-to-side portocaval or meso-caval shunts. In this situation, the mesoatrial has been claimed useful but the mortality is high because of a high rate of thrombosis. No agreement exists on which is the best approach when there is just compression but not obstruction of the inferior vena cava. Indeed, the most important is not the pressure gradient between the infra and supra hepatic part of the inferior vena cava, but the pressure gradient between the two territories to be connected (the portal and the cava veins) (32) The aim of surgical portosystemic shunting is twofold. Firstly, lowering of the portal pressure to physiologic values should resolve the ascites. Secondly, the shunt should function as a venous outflow for the increased intra hepatic portal pressure leading to improvement of the liver function and reduction of transaminase levels.

However, spontaneous improvements (5,24) and survivors after thrombosis of the surgical shunt (13,16) were observed suggesting an inconstant and transitional increase of intrahepatic portal pressure because of the development of collateral circulation (23).

Recently, asymptomatic BCS suggesting an inconstant increase of sinusoidal pressure were also observed (25) while the role of prothrombotic states and the usefulness of the anticoagulant therapy were emphasised (3,7,26).

Table 2. — **Investigations of prothrombotic states and types of shunts in patients treated with surgical portosystemic shun**

First Author (year of publication)	Number	Types of shunt	Investigation of prothrombotic states/Anticoagulation
Mitchell *et al*. (6) (1982)	6	meso-atrial	no
Franco *et al*. (14) (1985)	7	mesocaval, porto-atrial	yes/yes
Milkman *et al*. (27) (1985)	11	porto-caval, meso-caval, meso-atrial, spleno-renal, porto-caval ou meso-atrial	no
Gupta *et al*. (8) (1986[e])	2	porto-caval ou meso-atrial	no
Ahn *et al*. (20) (1986)	19	porto-caval, meso-caval, spleno-renal	non mentioned
Vons *et al*. (15) (1986)	9	meso-caval, porto-atrial, porto-caval + cavo-atrial	no
Klein *et al*. (12 (1989)	30	meso-caval, meso-atrial	no
Orloff *et al*. (18) (1989)		porto-caval	no
Wang *et al*. (28) (1989)	54	meso-atrial meso-caval, spleno-atrial, spleno-renal	no
Bismuth *et al*. (19) (1990)	22	porto-caval, meso-caval, meso-atrial	yes/yes
Orloff *et al*. (17) (1992)	33	porto-caval, meso-caval, porto-caval + cavo-atrial	no
Shaked *et al*. (10) (1992)	12	porto-caval, meso-atrial	yes/yes
Panis *et al*. (16) (1993)	25	porto-caval	yes/yes
Kholi *et al*. (13) (1993)	24	porto-caval, spleno-renal, meso-atrial	yes/no
Dilawari*et al*. (29) (1994)	15	porto-caval, meso-caval, meso-atrial	no
Ringe *et al*. (2) (1995)	9	porto-caval, meso-caval	yes/yes
Hemming *et al*. (27) (1995)	28	porto-caval,meso-caval, spleno-renal	yes/yes
Mamhoud *et al*. (24) (1996)	16	meso-caval, meso-atrial	yes/yes
Langlet *et al*. (3) (1998)	36	porto-caval, meso-caval	yes/yes
Zeitoun *et al*. (7) (1999)	82	porto-caval, meso-caval	yes/yes
Orloff *et al*. (32) (2000)	42	porto-caval, meso-caval, porto-caval + cavo-atrial	no/no

Severe BCS (with a high prognosis index, a high Child-Pugh-score and often acute-on-chronic form) are theoretically those with a great potential to get a benefit by decompressing the liver through a surgical shunt. However, the operative mortality of such high-risk patients may overcome the benefits of shunts. In the two only clinical studies attempting to assess the impact of surgical shunts on survival after adjustment on prognostic factors, we could not demonstrate any favourable effect (3,7).

Even if liver transplantation has been described as necessary in some patients with BCS treated by portosystemic shunt (11,27), controversy on what treatment should be applied to BCS has remained.

Discussion

Several retrospective studies comparing survival of patients with medical treatment and with surgical portosystemic shunt have lead their authors to the conclusion that portosystemic shunting is the procedure of choice (20,28,29). However, data concerning outcome of the BCS and results

of the different treatments should be taken with caution. Indeed, there is no randomised prospective study comparing surgical and medical treatment of BCS due to the scarcity of the disease.

Numerous factors of confusion limit the interpretation of results from studies concerning the outcome of patients treated with surgical portosytemic shunting.

Diversity of portosystemic shunts, post-operative follow-up, investigation and treatment of prothrombotic states (Table 2)

Some studies are homogeneous, including only porto or meso-caval shunts (2,3,7,16,18). Most studies, however, include patients treated with different portosystemic shunts including porto or meso-atrial shunts associated with worse results. This heterogeneity leads to difficult comparisons between studies.

Some studies include a great number of non-selected patients but have a short follow-up (2,28,29) whereas other studies include a limited number of patients (2,8,10,14,24), some with cancer (8,24,30).

In many studies, there is a lack of intensive investigation (6,15,17,18,28,29,31) or a lack of treatment of underlying prothrombotic states (13).

Adjustment on preoperative characteristics and control group of non-operated patients (Table 3)

In several retrospective studies**,** authors have concluded that portosystemic shunting is the procedure of choice in BCS (12-14,16-20,22,28,32). However, either there is no control group of medically treated patients (10,12-17,19,22) or the control group consists in patients for which surgical treatment was refused for clinical (20,28) or economical reasons (29). Results of these studies are presented in *table 4*. Analysis of these results clearly shows that overall perioperative mortality is very high suggesting that either patients have been operated in a to severe state or that the operation is associated with a deleterious effect.

Recently, we performed two studies assessing in a multivariate analysis the influence of surgical portosystemic shunting on survival after adjustment on prognostic factors in a non-selectioned sample of patients including control group (3,7).

In these two studies, after adjustment on prognostic factors (Child-Pugh score, age, ascites response to diuretics, serum creatinine) (3,7) and clinico-pathological variant of BCS (7), no significant impact of portosystemic shunt surgery on overall survival could be

Table 3. — **Adjustment on preoperative characteristics and non-operated control group**

First Author (year of publication)	Adjustment on preoperative characteristics	non-operated control group
Mitchell *et al*. (6) (1982)	no	6
Franco *et al*. (14) (1985)	no	0
Millikan *et al*. (27) (1985)	no	5
Gupta *et al*. (8) (1986[6])	no	13
Ahn *et al*. (20) (1986)	yes	12
Vons *et al*. (15) (1986)	no	0
Klein *et al*. (12) (1989)	no	0
Orloff *et al*. (18) (1989)	no	0
Wang *et al*. (28) (1989)	no	19
Bismuth *et al*. (19) 1990)	no	10
Orloff *et al*. (17) (1992)	no	0
Shaked *et al*. (10) (1992)	no	0
Panis *et al*. (16) (1993)	no	0
Kholi *et al*. (13) (1993)	no	0
Dilawari*et al*. (29) (1994)	no	150
Ringe *et al*. (2) (1995)	no	0
Hemming *et al*. (27) (1995)	no	0
Mamhoud *et al*. (24) (1996)	no	9
Langlet *et al*. (3) (1998)	yes	33
Zeitoun *et al*. (7) (1999)	yes	38
Orloff *et al*. (32) (2000)	no	no

demonstrated. This information associated with the high perioperative mortality suggests that the late beneficial effect of relieving congestion of portosystemic shunt to decrease portal hypertension could be balanced by an early deleterious effect of portal inflow deprivation (3,7). One may assume that the arterial buffer response might suppress the effect of portal decompression. Theses considerations remain hypothetical in the case of BCS.

Such dissociation would be reminiscent of surgical shunting in cirrhosis, which was proved to be very efficient in controlling ascites or gastrointestinal bleeding but not to prolong survival (33).These studies were not designed to answer the issue of symptomatic improvement and quality of life following shunting or medical therapy.

Further analysis should be performed to assess which patients should benefit from portosystemic shunt and which patients would have only deleterious effects. Using our data (3), a recent European clinico-pathological classification of BCS (table 1) taking into account clinical and histological data of BCS has been proposed. Indeed, uniform definitions and a standardised classification are of major importance, not only to enhance our understanding of the disease but also to facilitate future studies and disease management.

Because many diagnostic and therapeutic algorithms applied today are based on personal experience or data from a limited number of patients, it is difficult to propose clearly a specific treatment for a specific patient. Future multicentre prospective studies are necessary to clarify the place of medical treatment only, radiological treatment or portosystemic derivation.

A European prospective database to acquire the solid results that will guide us to the best interventions for this disorder will soon start.

Currently, we think that for patients with asymptomatic, acute, subacute or chronic BCS associated with a low prognostic index (PI < 5.4) (3,7) and a good liver function, medical treatment only (diuretics and anticoagulation) should be performed because the long term prognosis is excellent whatever the treatment applied (3). In a proportion of these patients with a short segment stenosis or occlusion of the hepatic veins with significant segments of patent hepatic vein or veins within the liver, angioplasty, stenting and thrombolysis could be highly desirable. This remains to be demonstrated in comparative studies.

In patients with an acute, chronic or most often acute-on-chronic BCS with a high prognostic index (PI > 5.4) and bad liver function, the prognosis is bad both with medical treatment and surgical portosystemic shunt. Liver transplantation is a live saving procedure in these patients.

What is the place of portosystemic derivation (surgical and TIPS) in the absence of overall survival improvement of surgical portosystemic shunting ?

Natural history of BCS (in absence of treatment) is unknown but has long been considered as progressive and almost uniformly fatal (5,6). However, the overall prognosis has improved in recent years (3,7,8). The actuarial survival rates in our recent study of more than 120 patients seen after 1985 are 91%, 82% and 79% at 1, 5 and 10 years. The long-term outcome of non-tumoral BCS in this cohort is better than that reported in previous series. This improvement can be explained by a better recognition of asymptomatic patients but also by a better recognition of underlying prothombotic disorders. This better recognition has allowed more systematic anticoagulant therapy (26) and a more accurate selection of patients to treat with surgical portosytemic shunting excluding patients with a severe liver failure.

No prospective randomised study has been designed to answer the issue of symptomatic improvement and quality of life following shunting because of the scarcity of BCS.

General clinical impression is that a good control of ascites is obtained with portosystemic shunt surgery if the patient has survived in the perioperative period ; a relapse of ascites usually corresponding to a stenosis or a thrombosis of shunt. This clinical impression has recently been confirmed in a non-controlled prospective study showing a good quality of life and a prolonged survival after portosystemic shunt surgery in patients without liver failure (32).

In patients with a chronic variant of BCS associated with a good Pugh score but with an important ascites, surgical or transjugular portosystemic shunts (TIPS) should be promptly considered to control disabling ascites persisting in spite of adequate medical management. Recently, several studies including limited patients have also shown encouraging results with TIPS

Table 4. — **Overall mortality, perioperative mortality, median follow-up**

First Author (year of publication)	Overall mortality	Perioperative mortality (at 1 year)	Median follow-up (months)
Mitchell *et al*. (6) (1982)	50%	20%	34
Franco *et al*. (14) (1985)	14%	0%	30
Millikan *et al*. (27) (1985)	28%	14%	not mentioned
Gupta *et al*. (8) (1986[6])	50%	50%	40
Ahn *et al*. (20) (1986)	46%	39%	not mentioned
Vons *et al*. (15) (1986)	11%	0%	34
Klein *et al*. (12) (1989)	35%	31%	43
Orloff *et al*. (18 (1989)	not mentioned	not mentioned	26
Wang *et al*. (28) (1989)	15%	8%	50
Bismuth *et al*. (19) (1990)	28%	9%	not mentioned
Orloff *et al*. (17) (1992)	5%	5%	60
Shaked *et al*. (10) (1992)	10%	5%	59
Panis *et al*. (16) (1993)	30%	30%	3-60
Kholi *et al*. (13) (1993)	38%	25%	30
Dilawari*et al*. (29) (1994)	31%	25%	32
Ringe *et al*. (2) (1995)	not mentioned	not mentioned	< 6
Hemming *et al*. (27) (1995)	50%	50%	49
Mamhoud *et al*. (24) (1996)	45%	35%	not mentioned
Langlet *et al*. (3) (1998)	13%	9%	30
Zeitoun *et al*. (7) (1999)	18%	13%	84
Orloff *et al*. (32) (2000)	6%	3%	82

in patients with liver failure as a bridge to hepatic transplantation (34,35). TIPS, a radiological interventional technique does not require laparotomy, is less invasive and seems to have the benefit of lower morbidity and operative mortality. This remains to be demonstrated in a larger clinical trials comparing surgery against TIPS.

Conclusions

Many diagnostic and therapeutic algorithms applied today are based on personal experience or data from a limited number of patients.

Uncertainty remains as to whether portosystemic shunting, which is considered the primary therapy for BCS, in fact improves the clinical outcome.

To assess the survival or the control of manifestations of patients with BCS, portosystemic shunt surgery should be compared with medical treatment alone, angioplasty, TIPS or transplantation.

A European prospective study will soon start using uniform definitions and a standardised classification.

While expecting these results, the place of portosystemic shunt surgery could be reserved to patients with a spontaneous good survival and mainly manifestations of portal hypertension. These patients are young patients without severe liver failure after angioplasty failure.

Liver transplantation should be considered as a live saving procedure in patients with liver failure whereas non-surgical treatment should be applied in other cases.

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