LIVER DISEASE

Acute propranolol administration effectively decreases portal pressure in patients with TIPS dysfunction

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Background and aims: Up to 60% of patients treated with transjugular intrahepatic portosystemic shunt (TIPS) require angioplasty or restenting during the first year of follow up because of TIPS dysfunction (stenosis of the intrahepatic shunt increasing the portal pressure gradient above the 12 mm Hg threshold). We hypothesised that in patients with TIPS stenosis, propranolol administration, by decreasing portal inflow, would markedly decrease portal pressure.

Patients and methods: Eighteen patients with TIPS dysfunction were investigated by measuring portal pressure gradient before and after acute propranolol administration (0.2 mg/kg intravenously; n=18).

Results: Propranolol markedly reduced the portal pressure gradient (from 16.6 (3.5) to 11.9 (4.8) mm Hg; p<0.0001), cardiac index (–26 (7)%), and heart rate (–18 (7)%) (p<0.0001). Portal pressure gradient decreased to less than 12 mm Hg in nine patients, more frequently in those with moderate dysfunction (portal pressure gradient 16 mm Hg) than in patients with severe dysfunction (portal pressure gradient >16 mm Hg) (8/10 *v* 1/8; p=0.015).

Conclusions: Propranolol therapy may delay the increase in portal pressure and reduce the need for reintervention in patients with TIPS dysfunction.

Transjugular intrahepatic portosystemic shunt (TIPS) is being widely used for the treatment of the complications of portal hypertension.[1–4] TIPS markedly reduces the portal pressure gradient (PPG) and is very effective in decreasing the risk of recurrent complications from portal hypertension.[1–5] Recent studies have shown that to offer adequate protection, TIPS should reduce and maintain PPG below 12 mm Hg.[5] However, PPG tends to increase during follow up owing to the development of stenosis or occlusion of the shunt.[3 5–7] This process is known as TIPS dysfunction, and is due to hyperplasia and fibrosis of the neointimal that covers the stent shunt.[5 8] TIPS dysfunction promotes the reappearance of portal hypertension and therefore the risk of recurrence of the complications of portal hypertension. Unfortunately, TIPS dysfunction occurs very frequently. Up to 60% of patients treated with TIPS will require angioplasty or restenting during the first year of follow up because of TIPS dysfunction.[1–9]

We hypothesised that in the setting of a stenosed TIPS, reducing splanchnic blood flow by means of propranolol administration should result in a marked fall in portal pressure and delay the increase in PPG above the threshold values for clinical complications.

Our study was designed to test this hypothesis by examining the effects of acute and long term propranolol administration on PPG and splanchnic and systemic haemodynamics in a series of patients with TIPS dysfunction.

PATIENTS AND METHODS

The study included 18 consecutive patients with cirrhosis that had a TIPS procedure because of variceal bleeding and who on follow up were found to have TIPS dysfunction. In six cases (three with oesophageal and three with gastric varices) TIPS was performed as a salvage procedure after lack of control by endoscopic and pharmacological means. In 12 cases (all with bleeding oesophageal varices) TIPS was performed as an elective procedure. TIPS dysfunction was demonstrated by the finding of a PPG >12 mm Hg at direct TIPS catheterisation.[5] TIPS dysfunction was considered to be moderate when the PPG was 12–16 mm Hg and severe when the PPG was >16 mm Hg. Clinical data on the patients studied are summarised in table 1

Table 1 Clinical data of patients with transjugular intrahepatic portosystemic shunt dysfunction included in the study

Age (y)	53 (11)
Aetiology of cirrhosis (alcoholic/non-alcoholic)	9/9
Child-Pugh score (points)	7.5 (1.6)
Child-Pugh class (A/B/C)	5/11/2
Ascites (yes/no)	6/12
Diuretic treatment (yes/no)	6/12
Platelet count (10^6/ml)	107 (65)
Haematocrit	0.32 (0.06)
Prothrombin ratio (%)	60 (13)
Oesophageal varices (small/big, %) (n=15)	33/77

The study was performed according to the principles of the Declaration of Helsinki and approved by the ethics committee for Clinical Research of the Hospital Clinic. The nature of the study was explained to the patients, and written informed consent was obtained in every case.

After an overnight fast, patients were transferred to the hepatic haemodynamic laboratory. Under local anaesthesia, a venous introducer was placed in the right jugular vein using the Seldinger technique. Under fluoroscopic guidance, a 7F catheter was advanced into the portal vein through the TIPS for pressure measurements and angiography. PPG was calculated as the difference between portal venous pressure and

Abbreviations: PPG, portal pressure gradient; HBF, hepatic blood flow; HR, heart rate; TIPS, transjugular intrahepatic portosystemic shunt; CI, cardiac index.

Table 2 Haemodynamic effects of acute propranolol administration (n=18)

	Baseline	Post-propranolol	p Value
Heart rate (bpm)	82 (13)	67 (10)	<0.0001
Cardiac index (l/min/m)	5.5 (1.0)	4.1 (0.8)	<0.0001
MAP (mm Hg)	82 (12)	80 (13)	NS
RAP (mm Hg)	6.6 (2.0)	10.3 (2.7)	<0.001
PPG (mm Hg)	16.6 (3.5)	11.9 (4.8)	<0.0001
PP (mm Hg)	25.6 (5.4)	23.6 (5.6)	<0.001
IVCP (mm Hg)	8.9 (3.3)	11.7 (2.5)	<0.0001
HBF (l/min)	0.50 (0.20)	0.44 (0.20)	<0.02

MAP, mean arterial pressure; RAP, right atrial pressure; PPG, portal pressure gradient; PP, portal pressure; IVCP, inferior vena cava pressure; HBF, hepatic blood flow.
All data are mean (SD).

inferior vena cava pressure. If angiography confirmed TIPS stenosis and PPG was >12 mm Hg, the patient was eligible for the study. In addition, a Swan-Ganz catheter (Abbott Laboratories, Chicago, Illinois, USA) was advanced into the pulmonary artery for measurement of cardiopulmonary pressures and cardiac output (thermal dilution). A solution of indocyanine green (ICG; Pulsion Medical Systems, Munich, Germany) containing 2% serum albumin was infused intravenously at a constant rate of 0.2 mg/min. After an equilibration period of at least 40 minutes, a 7F catheter was advanced into an hepatic vein, different from the one that had the TIPS, and four separate sets of simultaneous samples of peripheral and hepatic venous blood were obtained for measurement of hepatic blood flow (HBF), as previously described.[10] Shunt blood flow is not included in this calculation of HBF. All measurements were performed in triplicate, and permanent tracings were obtained on a multichannel recorder. Pressures are reported in mm Hg and cardiac output as cardiac index (CI) (litre×min/m^2). Mean arterial pressure was measured non-invasively with an automatic sphygmomanometer (MacLab, K74A0841J; Marquette, Milwaukee, Wisconsin, USA). Heart rate (HR) was derived from continuos electrocardiogram monitoring, and arterial oxygen saturation was monitored continuously by means of a pulse oximeter.

After completing baseline haemodynamic measurements, 18 patients received an intravenous propranolol infusion of 0.2 mg/kg in 10 minutes and all measurements were repeated 20 minutes later.[11] After completing these measurements, all patients received balloon angioplasty.

Statistics

Results are reported as mean (SD). Statistical analysis of the results was performed using the unpaired and paired Student's *t* test, ANOVA, and Fisher's exact test, as needed. Significance was established at p<0.05. All calculations were performed using the SPSS 9.0 statistical package (SPSS Inc., Chicago, Illinois, USA).

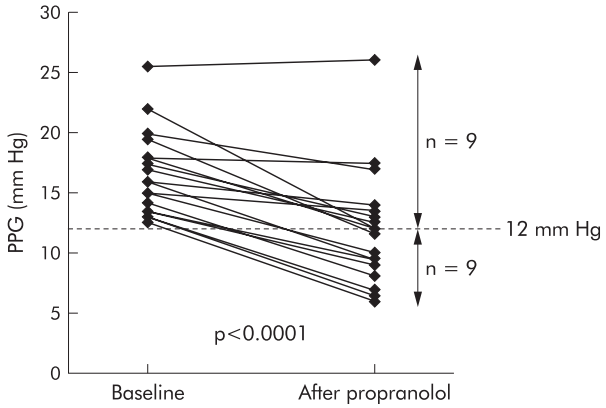

Figure 1 Individual values for portal pressure gradient (PPG) before and after acute administration of propranolol.

RESULTS

Clinical data of the patients are shown in table 1. The degree of TIPS dysfunction (baseline PPG) was similar in patients from Child-Pugh classes A, B, and C (16.8 (2.3), 16.8 (4.1), and 15.0 (2.8) mm Hg, respectively; NS)

Haemodynamic effects of acute propranolol administration

TIPS dysfunction was moderate in 10 patients and severe in eight. Acute propranolol administration caused a significant reduction in HR, CI, and HBF while mean arterial pressure was not modified (table 2). PPG decreased markedly (from 16.6 (3.5) to 11.9 (4.8) mm Hg, −30 (16)%; p<0.0001). Individual changes in PPG are shown in fig 1. As illustrated, PPG decreased below 12 mm Hg in nine of 18 patients (50%).

The proportion of patients with a decreasing PPG to <12 mm Hg was significantly greater among the 10 patients with moderate dysfunction than in the eight patients with severe TIPS dysfunction (80% *v* 13%; p=0.015) (fig 2). This was related to the lower baseline PPG of patients with moderate dysfunction (14.2 (1.3) mm Hg *v* 19.7 (2.9) mm Hg in severe dysfunction) as the mean fall in PPG was similar in both groups (4.8 (1.8) mm Hg or 35 (14)% in moderate dysfunction *v* 4.5 (3.6) mm Hg or 23 (17)% in severe dysfunction; NS). Patients with small varices (most with moderate dysfunction) had a greater fall in PPG than patients with big varices (−7.3 (3.1) mm Hg *v* −4.2 (2.2) mm Hg, respectively; p=0.08). There were no differences in the reduction in HBF, HR, or CI between patients with moderate or severe dysfunction (HBF −14 (15)% *v* −9 (14)%, NS; HR −16 (5) *v* −20 (8)%, NS; CI −25 (6) *v* −26 (9)%, NS).

The PPG response to propranolol was not different in patients with alcoholic compared with non-alcoholic cirrhosis (−24 (16)% *v* −34 (15)%, respectively; NS) and was not influenced by the degree of liver failure (−21 (12)% *v* −32 (18)% *v* −36 (14)% in Child-Pugh A, B, and C groups, respectively; NS).

Five of these patients with recurrent TIPS dysfunction despite repeated angioplasty (PPG 13.0 (2.6) mm Hg) were studied again after long term propranolol administration. After a mean of 3 (2) months, none had recurrent complications from portal hypertension, and PPG was below 12 mm Hg in four of these five patients (mean final PPG 10.5 (3.2) mm Hg; p<0.1 *v* baseline).

DISCUSSION

The portal pressure gradient is the result of the interaction of portal blood flow and the resistance that the portal hepatic vascular bed opposes to it. Increases in vascular resistance and

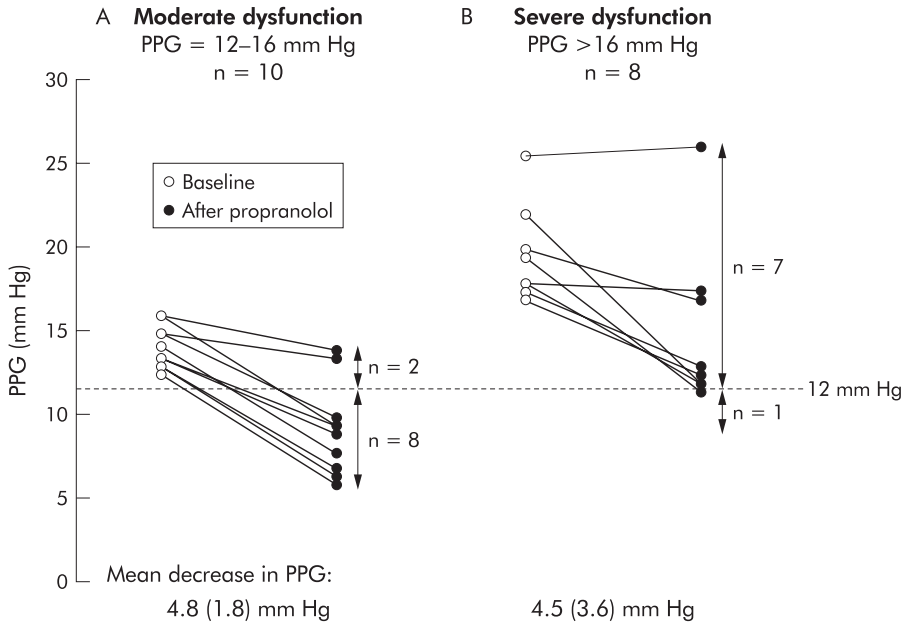

Figure 2 Individual values for portal pressure gradient (PPG) in patients with moderate and severe transjugular intrahepatic portosystemic shunt (TIPS) dysfunction. The number of patients with a decreasing PPG to below 12 mm Hg was significantly greater among those with moderate dysfunction than in those with severe TIPS dysfunction (8/10 *v* 1/8; p=0.015). This was due to the lower baseline PPG of patients with moderate dysfunction as the absolute fall in PPG was similar in both groups.

blood flow will raise the PPG. Conversely, reduction in vascular resistance and/or blood flow will decrease the PPG. Therapy for portal hypertension is based on these concepts.[12–14] Thus the use of beta adrenergic blockers, and vasopressin and somatostatin derivatives is based on the capacity of these agents to decrease portal blood inflow and thereby portal pressure.[14] Surgical portosystemic shunts,[15 16] and more recently TIPS,[1–6] illustrate the alternative approach in which the PPG is decreased by reducing the increased resistance to portal blood flow by means of bypassing the increased hepatic vascular resistance caused by cirrhosis.

Small diameter "calibrated" shunts[17] and TIPS[2 4] were introduced with the hope that they would be large enough to achieve a reduction in portal pressure sufficient to prevent or correct the complications of portal hypertension while being small enough not to be associated with an excessive risk of encephalopathy and liver failure. Many subsequent studies have confirmed that TIPS is indeed highly effective in the treatment of portal hypertension.[1 3 5 6] However, in contrast with surgical shunt, the reduction in PPG achieved by TIPS is not maintained over time, due to the very frequent development of TIPS dysfunction,[5–7] which calls for repeated reintervention to maintain the PPG below the 12 mm Hg threshold value for the appearance of complications of portal hypertension.[5 18 19] Indeed, a previous study from our laboratory showed that TIPS dysfunction—defined as an increase in PPG above 12 mm Hg—occurs in up to 80% of patients and that up to 70% required reintervention.[5] The reported incidence of TIPS dysfunction varies among studies due to different definitions or cut off values, but in a recent meta-analysis of nine randomised controlled trials averaged 50% at one year.[9] When TIPS dysfunction develops, the only successful treatment to date is reintervention, using balloon angioplasty and in some cases restenting. This is indeed a major caveat of TIPS.[20–22]

In this study, we examined if a simple inexpensive therapy, such as administration of propranolol, could diminish the haemodynamic consequences of TIPS dysfunction. Indeed, our results demonstrated that propranolol markedly reduced the PPG in patients with TIPS dysfunction. In fact, the decrease in PPG was so marked that 50% of patients reduced the PPG to below the 12 mm Hg threshold. This was specially evident in patients with moderate dysfunction in which 80% had such an optimal response, suggesting that propranolol therapy may be adequate to maintain the PPG in the safe range in a large proportion of patients with moderate TIPS dysfunction. Therefore, our findings suggest that propranolol administration may decrease the haemodynamic consequences of TIPS dysfunction and thus decrease the frequency by which these patients will require reintervention. Also, it can be proposed that adding propranolol therapy to all patients treated by TIPS may delay the reappearance of significant portal hypertension after TIPS. This concept is supported by the results obtained in our five patients with recurrent TIPS dysfunction that were treated with long term propranolol administration. Obviously, the real value of concomitant beta blocker therapy in this situation should be evaluated objectively in randomised controlled trials. The fact that reintervention is both costly, invasive, and demanding, and that propranolol is safe and inexpensive adds priority to such a study. Another situation where the current findings may have practical implications is for the occasional patient who fails to lower the PPG to below 12 mm Hg following TIPS.

The reduction in the PPG after propranolol observed in our patients with TIPS dysfunction exceeds markedly what is usually observed in patients with cirrhosis and portal hypertension not treated with TIPS. Many studies have shown that only about one third (or less) of these patients will exhibit a marked haemodynamic response, as defined by a fall in PPG to below 12 mm Hg or over 20% of baseline values.[14 18 19 23 24] The very pronounced decrease in the PPG in patients with TIPS dysfunction may involve several mechanisms. The fall in CI and HR observed in our patients was similar to previous studies in patients without TIPS,[18 19 23 24] so the degree of beta blockade is not an explanation. However, it is worth emphasising that the portal pressure response to propranolol is markedly influenced by the effects of beta blockade on portal collateral resistance.[25] Collateral resistance is increased by beta blockers, which means that the fall in PPG is less marked than the decrease in portal collateral blood flow.[25] In contrast, intrahepatic resistance is not markedly influenced by propranolol.[26] This is thought to be the reason why cirrhotics

with portal hypertension but without varices, with a limited extent of collateralisation, exhibit a more pronounced decrease in PPG than patients with varices.[27] Patients with TIPS behave as cirrhotics with little amount of collaterals as TIPS markedly decreases the size of varices and the extent of extrahepatic portal systemic shunts[5] that may constrict under beta blockers.[25 28] Even in patients that have developed TIPS dysfunction, especially when this is moderate, it is likely that the extent of extrahepatic collaterals is still below what it was before TIPS.

On the other hand, TIPS is know to worsen the hyperkinetic circulation of cirrhosis[29] which is likely to be due to enhanced release of nitric oxide induced by shear stress.[30 31] This is another explanation for the favourable effects of propranolol in patients with TIPS as propranolol administration markedly attenuates the hyperkinetic syndrome.

Another issue to consider is whether propranolol therapy may influence the degree or likelihood of post-TIPS encephalopathy. Certainly, by decreasing splanchnic blood flow propranolol will decrease the absolute amount of shunt blood flow.[24] However, it is likely that rather than absolute shunt flow, post-shunt encephalopathy is influenced by relative shunt flow—the fraction of portal blood flow not perfusing functional liver tissue—which is probably not increased by beta blockade. Although none of our patients included in the long term administration study had encephalopathy during the study period, this issue requires further study.

In summary, the present study demonstrated that in patients with TIPS dysfunction, propranolol administration markedly decreased the PPG to the point that a large proportion of patients achieved values well below the 12 mm Hg threshold for clinical complications. This was especially true among patients with moderate TIPS dysfunction. The results of this study suggest that concomitant propranolol therapy may decrease the need for reintervention in TIPS treated patients, and provides the rationale for testing this hypothesis in appropriate randomised clinical trials.

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