

Somatostatin and Propranolol to Treat Small-for-Size Syndrome that Occurred Despite Splenic Artery Ligation

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We report our success with somatostatin and propranolol to treat small-for-size syndrome that occurred despite splenic artery ligation. A 48-year-old woman with cirrhosis due to autoimmune hepatitis underwent living-donor liver transplant; her graft-to-body weight ratio of the right lobe was 0.91%. After arterial reperfusion, portal pressure and flow were 24 cm H₂O and 2.22 L/min (ie, 360 mL/100g graft/min), respectively. Following splenic artery ligation, the portal pressure decreased to 16 cm H₂O and portal flow to 1.74 L/min (ie, 282 mL/100g graft/min). On the second postoperative day, small-for-size syndrome was diagnosed based on the marked prolongation of prothrombin time (international normalized ratio, 4.4), hyperbilirubinemia (359.1 micromol/L), rapid escalation of transaminases (alanine aminotransferase 2488 U/L, aspartate aminotransferase 1075 U/L) and very high portal flow rate (> 90 cm/sec). Oral propranolol (40 mg/day b.i.d.) and somatostatin infusion (250-μg bolus followed by perfusion at a rate of 250 μg/h for 5 days) were started. Prothrombin time and transaminase levels began to decrease the following day, although the bilirubin level increased to 495.9 μmol/L before returning to normal. The patient was discharged in excellent health 5 weeks after surgery. Despite reduction of portal pressure by splenic artery ligation, small-for-size syndrome may develop in patients with persistent high portal flow. To the best of our knowledge, this is the first report of the successful treatment of small-for-size syndrome by somatostatin and propranolol in the clinical setting.

Key words: Liver transplant, Living donor, Somatotropin release-inhibiting factor

Small-for-size syndrome after liver transplant is thought to develop primarily from portal hyperperfusion injury, that is, disruption of the portal bed of the "small" graft by excessive flow (1-5). In the clinical setting, surgical manipulations that decrease portal flow have been used to prevent or treat small-for-size syndrome (6-17). In some of these reports, portal pressure after arterial reperfusion has been used as a surrogate marker of how well the graft can "accommodate" the portal flow (6, 8, 18, 19). A level of 20 mm Hg (or 25 cm H₂O in 1 paper) has been proposed as a critical threshold for flow modulation (6, 18, 19). On the other hand, Troisi and associates used intraoperative blood flow measurements to define hyperperfusion (10, 11), and proposed that a graft portal flow higher than 250 mL / 100g graft/min should be an indication.

In experimental studies, pharmacologic manipulation of portal hemodynamics by FK 409 (20) and somatostatin (21) has been shown to improve survival after transplant of small-for-size grafts. In 1 clinical study on 4 small liver graft recipients, infusions of octreotide (for 6 hours alone) and esmolol (for another 6 hours, with octreotide) showed additive effects in alleviating portal hyperperfusion; however, the clinical outcomes of the patients were not reported (22).

Despite the rapid expansion of living-donor liver transplant in the adult population over the last few years, small-for-size syndrome has emerged as a significant clinical problem. In this paper, we report our success with somatostatin and propranolol to treat small-for-size syndrome that occurred in a patient despite splenic artery ligation.

Case report

A 48-year-old woman with cirrhosis due to autoimmune hepatitis underwent a living-donor liver

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transplant with a graft from her daughter. The recipient was 165 cm tall and weighed 68 kg (1.5 L of ascites were aspirated on laparotomy). Her Child-Pugh score was 8 and her MELD score was 18. She had undergone endoscopic treatment for variceal hemorrhage and was taking propranolol (40 mg b.i.d.) to prevent recurrent bleeding.

The donor was a 20-year-old woman in excellent health. Her preoperative liver biochemistry values and results of a biopsy specimen were normal. The donor operation was uneventful; there was no episode of hypotension, and a blood transfusion was not required. The right lobe graft without the middle hepatic vein weighed 616 g; graft-to-body weight ratio was 0.91%.

A temporary portocaval shunt was used during the recipient hepatectomy. The graft was implanted by side clamping the inferior vena cava. The superior and inferior right hepatic veins as well as a large segment 5 vein (V5) were reconstructed. The cold ischemia time was 65 minutes, and warm ischemia time was 70 minutes. She had a large superior mesenteric vein-adrenal vein shunt that was left undisturbed. The graft artery was anastomosed to the recipient right hepatic artery. After arterial reperfusion, portal pressure and flow (HT 323 flow meter, Transonic Systems Inc., Ithaca, NY, USA) were 24 cm H₂O and 2.22 L/min (ie, 360 mL/100g graft/min) respectively. The splenic artery was ligated along the upper border of the pancreatic body. The portal pressure decreased to 16 cm H₂O and portal flow decreased to 1.74 L/min (282 mL/100g graft/min). The graft bile duct was anastomosed to the recipient hepatic duct over 2 transcholedochal stents inserted into the anterior and posterior sectional ducts. The immunosuppressive regimen included a steroid, basiliximab (on days 0 and 4), tacrolimus (started on the fifth postoperative day), and mycophenolate mofetil.

The patient was extubated on the first postoperative day. Her laboratory values were as follows: international normalized ratio 3.1, total bilirubin 309.5 μ mol/L (preoperative level: 22.2 μ mol/L), direct bilirubin 165.9 μ mol/L, alanine aminotransferase 374 U/L, aspartate aminotransferase 264 U/L. Doppler ultrasonography showed patent right superior and inferior hepatic veins, V5, portal vein, and hepatic artery with normal flow patterns; however, the flow rate in the portal vein was higher than 90 cm/sec. There was no biliary dilation. On the second postoperative day, the international normalized ratio was 4.4, the total bilirubin level was 359.1 μ mol/L, the direct bilirubin level was 256.5 μ mol/L, the alanine aminotransferase

level was 2488 U/L, and the aspartate aminotransferase level was 1075 U/L. Doppler ultrasonography findings were similar to those of the first day. There was no sign of infection. Drug toxicity was considered unlikely. In light of the operative findings and the postoperative course, small-for-size syndrome was diagnosed. Oral propranolol (40 mg b.i.d.) and a somatostatin infusion (250- μ g bolus followed by perfusion at a rate of 250 μ g/h) were started. Also, an intravenous N-acetyl-cysteine infusion (100 mg/kg/day for 5 days) was given. The international normalized ratio and transaminase levels started to decrease on the following day although the bilirubin level increased up to 495.9 μ mol/L before returning to normal levels. Blood and urinary cultures remained sterile. Somatostatin infusion (5 days) was stopped on the seventh postoperative day; her laboratory data at that time were as follows: international normalized ratio, 1.6; total bilirubin, 215.5 μ mol/L; direct bilirubin, 165.9 μ mol/L; alanine aminotransferase, 250 U/L; aspartate aminotransferase, 27 U/L. She was discharged in excellent health 5 weeks after surgery with oral propranolol treatment.

Discussion

Although small-for-size syndrome is a multifactorial process dependent on recipient, donor, and surgery-related factors, it is generally accepted that portal hyperperfusion injury is the overriding factor (1-5). Accordingly, surgical manipulations that decrease portal flow have been used to prevent or treat small-for-size syndrome (6-17). On the other hand, because adequate portal flow is vital for graft function, the critical issue is how portal perfusion can be assessed reliably and reproducibly. In other words, "overcorrection" could be even more detrimental. Some authors have used portal pressure after arterial reperfusion as a guide (6, 8, 18, 19), whereas Troisi and associates used portal flow measurements (10, 11). Yagi and associates measured both pressure and flow and stated that they ligated spontaneous collaterals to maintain portal flow higher than 800 mL/min but gave priority to keeping the portal pressure below 20 mm Hg in their intraoperative decisions (19).

In the patient reported here, portal pressure and flow after arterial reperfusion, were 24 cm H₂O and 2.2 L/min (ie, 360 mL/100g graft/min), respectively. She had a large portosystemic collateral vein between the superior mesenteric and adrenal veins. Some authors have advocated that to ensure adequate flow to the graft (19, 23) and even to prevent hepatofugal flow in some patients (24), ligation of large portosystemic

shunts should be considered during liver transplant. Because the portal pressure and flow were high in spite of the patent shunt, the natural shunt of our patient was left undisturbed. Ligation of the splenic artery decreased the portal pressure to 16 cm H₂O and portal flow to 1.74 L/min (282 mL/100g graft/min). These values created an intraoperative dilemma. The initial portal pressure was close to, but lower than, the upper value of the "safe" range (< 20 mm Hg, approximately 27 cm H₂O); however, the portal flow was nearly one and a half times as fast as the critical threshold (250 mL/100g graft/min). After splenic artery ligation, the portal pressure decreased significantly but flow remained above 250 mL/100g graft/min. Considering that portal pressure measurements are less prone to variations in the respiratory and cardiac cycles than are flow measurements, and that further reductions in portal pressure could precipitate portal thrombosis, we performed no other maneuver. However, obvious small-for-size syndrome developed postoperatively. This observation shows that portal pressure alone is an inadequate parameter, and further studies examining both portal pressure and portal flow are required to establish guidelines for this complicated problem.

Experimental studies have shown that pharmacologic manipulation of portal hemodynamics by FK 409 (20) and somatostatin (21) improves survival after transplant of small-for-size grafts. However, there is only 1 related clinical study of 4 small liver graft recipients (22). In 3 patients, infusions of octreotide (for 6 hours alone) and esmolol (for another 6 hours with octreotide) showed additive effects in alleviating portal hyperperfusion; 1 patient received octreotide alone but experienced hemodynamic instability. However, it is not clear whether the infusions were continued beyond 6 hours, and neither pretreatment conditions nor the clinical outcomes of the patients were reported (22).

Propranolol and somatostatin both decrease portal flow and pressure reliably and reproducibly in patients with cirrhosis. Propranolol and somatostatin are widely used to treat and prevent variceal bleeding (25). Although there was a potential risk of overtreatment, in view of the critical situation of our patient, both agents were used simultaneously for 5 days. The portal flow rate measured by Doppler ultrasonography decreased after treatment but remained at adequate levels (50-70 cm/sec). The recovery of liver function was gratifying.

In conclusion, in patients with persistent high portal flow, small-for-size syndrome may develop despite reduction of portal pressure by splenic artery

ligation. To the best of our knowledge, this is the first report the successful treatment of small-for-size syndrome using somatostatin and propranolol in the clinical setting.

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