Abstract:

Pulmonary arterial pressure management based on oral medicine for pediatric living donor liver transplant with portopulmonary hypertension

Pediatric living donor liver transplantation (LDLT) in patients with advanced portopulmonary hypertension (PoPH) is associated with poor prognosis. Recently, novel oral medications, including endothelin receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors and oral prostacyclin (PGI2) have been used to treat PoPH. Pediatric patients with PoPH who underwent LDLT from 2006 to 2016 were enrolled. Oral pulmonary hypertension (PH) medication was administered to control pulmonary arterial pressure (PAP). Four patients had PoPH. Their ages ranged from 6 to 16 years, and their original diseases were biliary atresia (n = 2), portal vein obstruction (n = 1), and intrahepatic portal systemic shunt (n = 1). For preoperative management, 2 patients received continuous intravenous PGI2 and 2 oral medications (an ERA alone or an ERA and a PDE5 inhibitor), and 2 received only oral drugs (an ERA and a PDE5 inhibitor). One patient managed only with intravenous PGI2 died. In the remaining 3 cases, intravenous PGI2 or NO was discontinued before the end of the first postoperative week. Postoperative medications were oral PGI2 alone (n = 1), an ERA alone (n = 1) or the combination of an ERA and a PDE5 inhibitor (n = 1). An ERA was the first-line therapy, and a PDE5 inhibitor was added if there was no effect. New oral PH

medications were effective and safe for use in pediatric patients following LDLT. In particular, these new oral drugs prevent the need for central catheter access to infuse PGI2.

Pulmonary arterial pressure management based on oral medicine for pediatric living donor liver transplant with portopulmonary hypertension

Introduction

Portopulmonary hypertension (PoPH), one of several pulmonary vascular disorders complicating chronic liver disease, [1] is defined by elevated mean pulmonary arterial pressure (PAP), increased pulmonary vascular resistance, and normal pulmonary capillary wedge pressure in the presence of portal hypertension. [2] The condition is characterized by vascular obstruction and increased resistance to pulmonary arterial flow due to varying degrees of pulmonary endothelial and smooth muscle proliferation, vasoconstriction, and in situ thrombosis. [3]

Pediatric living donor liver transplantation (LDLT) has a poor prognosis in patients with advanced PoPH. Therefore, untreated moderate-to-severe PoPH is considered a contraindication to liver transplantation (LT). [4, 5] To achieve successful LT it is important to manage pulmonary hypertension (PH) by controlling perioperative PAP. Recently, novel oral medications, including endothelin receptor antagonists (ERAs), phosphodiesterase 5 (PDE5) inhibitors, and oral prostacyclin (PGI2) have been developed to treat PH. Here we report the effect of these drugs in the setting of pediatric LDLT.

Methods

Patients with PoPH who underwent LDLT at our institution from 2006 to 2016, and who were under 18 years old at the time of LDLT, were identified. Patients received a standard tacrolimus formulation with a steroid taper. No patients were withdrawn from immunosuppressive therapy.

Cardiac ultrasound was performed during pre-transplant evaluation. Other cardiopulmonary diseases, but not liver disease, were excluded for possible primary pulmonary hypertension. Finally, mean PAP was evaluated by cardiac catheterization to diagnose PH. A mean PAP over 25 mmHg was diagnosed as pulmonary hypertension. Intraoperative PAP was monitored with a Swan-Ganz catheter.

Medications for PoPH were administered to control PAP prior to LDLT. Medications for PoPH was ultimately primarily be at the discretion of the treating physicians and was decided by clinical needs in the interest of the individual patient. Patients' medical records were reviewed retrospectively to collect the following data: perioperative medications, intraoperative management and outcomes.

Data were analyzed using the JMP Ver.11 software package (SAS, Cary, NC, USA). Continuous variables are presented as median values with ranges and compared using Student's t-test. A *P* value less than .05 was considered to be statistically significant.

Results

Four patients who underwent LDLT had comorbid PoPH. Their ages were 6 to 16 years old, and their original diseases were biliary atresia (n = 2), portal vein obstruction (n = 1) and intrahepatic portal systemic shunt (n = 1). Three patients were asymptomatic, while 1 patient complained of dyspnea. Patient characteristics are shown in Table 1. The perioperative clinical course of case 4, who had an intrahepatic portal systemic shunt, is shown in Fig 1.

The mean pre-treatment PAP was 45.5 mmHg (range, 41–51 mmHg). For preoperative management, 2 patients received continuous intravenous PGI2 and 2 oral medications (an ERA and a PGE5 inhibitor), and 2 patients received only oral drugs. An ERA alone or an ERA and a PGE5 inhibitor were chosen as oral medications for PoPH. An ERA was the first-line therapy, and a PGE5 inhibitor was added when there was no effect. LDLT was performed after the mean PAP reached 35 mmHg or less. The mean pre-transplant PAP was 30 mmHg (range, 24–34 mmHg) (Fig 2), a significant decrease from the pre-treatment level (P= .005). Furthermore, oral PH medication was sufficiently effective as pre-transplant treatment in cases 3 and 4, and intravenous PGI2 was therefore not required (P= .05).

Intraoperative management was performed using intravenous PGI2 (n = 2) or nitric

oxide (NO) inhalation (n = 2). Intravenous PGI2 was administered at the pre-transplant doses. NO was inhaled at 10–20 ppm. The maximum mean PAP intraoperatively was 42.3 mmHg (range, 39–45 mmHg)

Oral medications were resumed via nasogastric tube on the day after surgery. One patient who was treated with intravenous PGI2 alone died after LDLT. In the remaining 3 cases, intravenous PGI2 or NO inhalation was discontinued before the end of the first postoperative week. Postoperative medications were oral PGI2 alone (n = 1), an ERA alone (n = 1) or the combination of an ERA and a PGE5 inhibitor (n = 1).

Case 1 died from graft failure at 1 month after LDLT due to primary non function. However, PoPH improved in the other 3 cases, and oxygen inhalation was reduced or stopped. Oral PH medication was continued until now. Tacrolimus levels were well controlled. There were no complications related to the oral PH medications.

Discussion

PoPH is best defined as pulmonary arterial hypertension associated with portal hypertension, whether or not the portal hypertension is secondary to an underlying liver disease. Once pulmonary hypertension is diagnosed, LT is one of remaining therapy in most cases.

However, mortality rates after LT are not low. In patients with a mean PAP >35 mmHg, the mortality rate was over 50%. [6] According to the European Respiratory Society Task Force, patients with a mean PAP <35 mmHg can undergo LT without preoperative medical treatment, those with a mean PAP of 35 to 45 mmHg should receive vasodilator therapy before LT, and those with a mean PAP >45 mmHg should receive vasodilator therapy only. [2] These results were in the era pre oral PH medications.

The treatment effects and impact on those considered for LT require further characterization by well-designed prospective studies before practice guidelines can be suggested. [7] Ogawa et al performed an acute volume challenge test to evaluate right ventricular function when the mean PAP after treatment (including prostacyclin) was <40 mmHg or the initial mean PAP without therapy was <35 mmHg. They performed LDLT when the mean PAP after anesthetic induction was confirmed to be ≤35 mmHg. LDLT has major benefits for biliary atresia patients with well-controlled portopulmonary hypertension. [8] In our cases, LDLT was delayed until patients with PoPH had a mean PAP <35 mmHg.

The aims of therapy in patients with PH are based on the 3 pathways involved in pulmonary vasoconstriction and vascular remodeling: the PGI2, NO, and endothelin pathways. [9] PGI2 derivatives are potent pulmonary and systemic vasodilators, and they have antiplatelet aggregating and antiproliferative effects. In idiopathic PH, these properties

can improve hemodynamics and increase exercise tolerance. [10] The most commonly used PGI2 is epoprostenol (intravenous PGI2), and it is often administered before LT. The use of the oral synthetic prostanoid beraprost reduced PAP and resulted in sustained improved symptoms in cirrhotic patients with PoPH. [11]

Endothelin-1 levels in plasma have been reported to correlate with the severity of liver cirrhosis and PH. [12]Endothelin-1 is up-regulated in cirrhotic patients with PoPH. [13] The liver function of patients with PoPH should be monitored closely during ERA therapy because these agents have been associated with hepatotoxicity in unselected patients with idiopathic PH. [14]

PDE5 inhibitors inhibit the growth of pulmonary vascular smooth muscle cells and lower mean PAP and pulmonary vascular resistance, mediating vasodilation through guanosine monophosphate. [15] Sildenafil can cause splanchnic vasodilation and increase portal hypertension by preventing the breakdown of cyclic guanosine monophosphate, leading to NO–induced vasodilation of the vascular pulmonary bed; therefore, it should be used carefully. [16] PGE5 inhibiters are a first-line treatment in patients with idiopathic PH. However, they may result in systemic hypotension or maintain portosystemic shunts due to their systemic effect. At our institution, an ERA is the first choice for PoPH, and a PGE5 inhibiter is added if necessary.

NO is a selective vasodilator that can be administered via inhalation. In mild cases of portopulmonary hypertension, it can be useful perioperatively. [17] In our study it was used for intraoperative management in patients not treated with intravenous PGI2.

Bosentan, first oral ERA, was commercially available since 2005 in Japan. Sildenafil, first oral PGE5 inhibiter, is commercially available since 2008 in Japan. [18]Many oral PH medications were released. Treatment and prognosis of PoPH has been dramatically improved. Stabilization or reversibility of PoPH seems to be an attainable goal using the combination of PH medications.[19]

In this era of new oral medications for PoPH, when the condition occurs in isolation, it no longer represents a valid indication for LT. Instead, LT should be performed in patients with liver failure and comorbid mild PoPH who meet the required criteria. In this study, oral PH medications were effective in pediatric patients undergoing LDLT, and peri-transplant PoPH could be managed without intravenous PGI2.

Conclusions

New oral PH medications were effective and safe in the setting of pediatric LDLT. In particular, these new oral drugs prevent the need for central catheter access to infuse intravenous PGI2.

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