

## What do we take consideration in the patient who has an unpredicted severe portopulmonary hypertension in liver transplantation? -a case report-

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Severe portopulmonary hypertension (PPHT) is considered a contraindication for liver transplantation (LT) because of the associated high mortality and poor prognosis. We report the case of a 57-year-old cirrhotic woman with severe PPHT (mean pulmonary artery pressure [mPAP] > 65 mmHg), who underwent a successful living donor LT. Intra-operative use of inhaled iloprost, milrinone, dobutamine, and postoperative use of inhaled nitric oxide and oral sildenafil failed to lower the pulmonary artery pressure (PAP). The patient responded only to nitroglycerin and drainage of massive ascites. Meticulous intra-operative volume control, which included minimizing blood loss and subsequent transfusion, was carried out. The use of vasopressors, which may have elevated the PAP, was strictly restricted. Intra-operative PAP did not show an increase, and the hemodynamics was maintained within relatively normal range, compared to the preoperative state. The patient was discharged without any complications or related symptoms. (Korean J Anesthesiol 2015; 68: 83-86)

**Key Words:** Ascites, Liver transplantation, Nitroglycerin, Portopulmonary hypertension.

Portopulmonary hypertension (PPHT) occurs in up to 4.5–8.5% of the patients with end stage liver disease (ESLD) [1,2]. It can occur regardless of portal hypertension. Its prognosis is fatal with a median survival of 15 months with treatment and 6

months without treatment [3]. Aggressive treatment is therefore required immediately on detection. PPHT goes undiagnosed in many patients until a pulmonary artery catheter is inserted as a part of the anesthetic procedures during surgery, and also, the available evidence that would guide decision-making on whether to proceed with liver transplantation (LT) when severe PPHT is detected is scant [4]. Here, we present the case of a patient who did not respond to pulmonary vasodilators such as inhaled iloprost, milrinone, dobutamine, and oral sildenafil, but successfully underwent LT with management of the pulmonary artery pressure (PAP) increase as well as meticulous intraoperative volume control and restriction of vasopressors.

### Case Report

A 57-year-old woman (height 152 cm, body weight 75 kg) was

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Received: July 1, 2014.  
Revised: August 2, 2014.  
Accepted: September 8, 2014.

Korean J Anesthesiol 2015 February 68(1): 83-86  
<http://dx.doi.org/10.4097/kjae.2015.68.1.83>

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scheduled for a living donor LT. She had liver cirrhosis (Child-Pugh score, 11; Model for End-stage Liver Disease [MELD] score, 24) secondary to NCNB (non C non B) accompanied by underlying diseases such as chronic kidney disease and diabetes mellitus. She had recurrent ascites, severe esophageal and gastric varices, and spontaneous bacterial peritonitis. She showed a mild tricuspid regurgitation with moderate pulmonary hypertension (PHT) and right ventricle systolic pressure (RVSP) of 59 mmHg with preserved RV contractility on preoperative cardiac echocardiography. She was diagnosed with portopulmonary hypertension (PPHT), and treatment was initiated with oral sildenafil 20 mg for 5 days until LT. The preoperative RVSP was maintained with this treatment and showed no deterioration. She did not present any symptoms related to PHT and right heart dysfunction. We proceeded with LT as scheduled. Anesthesia was induced with intravenous propofol 80 mg and rocuronium bromide 50 mg and maintained with 1.0 L/min of air, 3.0 L/min of O<sub>2</sub>, and desflurane 4 vol% with continuous infusion of remifentanyl and atracurium. A Swan-Ganz Catheter (Swan-Ganz, CCombo Volumetrics, Edwards Lifesciences, Irvine, CA, USA) was inserted through a right IJV 9-Fr introducer (Edwards AVA high-flow device, Edwards Lifesciences, Irvine, CA, USA). We advanced this catheter into the pulmonary artery through the right ventricle; the PAP was 107/43 mmHg, mean pulmonary artery pressure (mPAP) was 68 mmHg, central venous pressure (CVP) was 17 mmHg, pulmonary vascular resistance (PVR) was 733 dyne·sec/cm<sup>5</sup>, and pulmonary capillary wedge pressure (PCWP) was 13 mmHg. Other hemodynamic parameters were relatively stable as follows: blood pressure, 121/70 mmHg; heart rate, 66 beats/min; cardiac output (CO), 4.7 ml/min; systemic vascular resistance (SVR), 868.09 dyne·sec/cm<sup>5</sup>; and SpO<sub>2</sub>, 92%. We first thought that this unpredicted high PAP was due to a mechanical problem such as kinking of the catheter or its attachment to a vascular wall, or a malfunctioning device. We reinserted a new catheter, but it again presented a high PAP of 106/48 mmHg with an mPAP of 67 mmHg and CVP of 16 mmHg. Even though severe PPHT was considered a contraindication for LT, we proceeded with LT for the following reasons: First, there were no preoperative symptoms or signs related to PHT. Second, we were able to predict that she would respond to intraoperative pulmonary vasodilators because mPAP was lowered up to 50 mmHg by nitroglycerin 200 µg bolus administration. Lastly, we expected that mPAP would be decreased by ascites drainage as she had massive ascites. As expected, about 9,000 ml of ascitic fluid was drained. Mean PAP, CVP, systolic PAP, and PVR were lowered to 42 mmHg, 9 mmHg, 65 mmHg, and 257.8 dyne·sec/cm<sup>5</sup>, respectively, following ascites drainage. We administered nitroglycerin 0.1–1.0 µg/kg/min, dobutamine 3 µg/kg/min, and milrinone 0.3–1 µg/kg/min throughout the surgery; 2.5 µg of inhaled iloprost (Ventavis<sup>®</sup> inhaler, Schering Korea, Seoul, Korea) was

administered three times: before surgery, 1 hour after the start of surgery, and before reperfusion. The iloprost vaporizer diluted in 5 ml normal saline was connected to the proximal limb of the inspiration circuit. However, these drugs neither decreased nor prevented an increase of mPAP and PVR.

The surgical team including the anesthesiologist and surgeons carefully managed the entire process. We reminded the surgeons of the intraoperative right heart failure risk before the surgery and advised them to minimize blood loss during the surgery. With regard to anesthesia, we restricted the use of vasopressors as much as possible to prevent the rise of intraoperative PAP and minimized volume infusion to the extent that allowed maintenance of normal hemodynamic parameters. Intravenous fluids were given to maintain CVP between 5 and 10 mmHg. Crystalloid solutions including 0.45% sodium chloride and Normosol-R pH 7.4 (plasma solution A, CJ plasma, Eumseong, Korea), hydroxyethyl starch (6%; 130/0.4) solution (Voluven<sup>®</sup>, Fresenius Kabi, Bad Homburg, Germany) and 20% albumin were used when intravascular volume expansion was urgently needed. End-tidal carbon dioxide (CO<sub>2</sub>) was maintained at a low level of 25–30 mmHg for pulmonary vasodilation. In reperfusion period, the hemodynamic parameters were relatively stable without excessive bleeding and needs for vasoactive agents. The total operating time was 6 hours 48 minutes; systolic PAP was 55–105 mmHg, mPAP was 40–65 mmHg, PVR was 318–733 dyne·sec/cm<sup>5</sup>, PCWP was 11–13 mmHg, and CO was 6.0–9.8 ml/min during the entire procedure. Reperfusion syndrome was very transient; the lowest systolic blood pressure was about 70 mmHg, and it was recovered in about 2 minutes without special medical treatment. To avoid volume overload, we set the volume status as a negative balance. The total input was 8,800 ml; 4,050 ml (packed RBC 2,250 ml and fresh frozen plasma 1,800 ml) of transfusion and 4,750 ml of fluid including crystalloids and colloids. The total output was 12,900 ml with 200 ml of urine, 9,000 ml of ascites, and 3,700 ml of blood loss. This patient was continued on dobutamine, nitroglycerin, and milrinone for 6 postoperative days. After arriving at the ICU, her systolic PAP, mPAP, and CVP were still high at 81 mmHg, 52 mmHg, and 10 mmHg, respectively. Therefore, as additional treatments, we applied nitric oxide (NO) ventilation at 16 ppm and 10 µg of iloprost inhaler daily. Moreover, 25 mg of oral sildenafil with 5 mg of ambrisentan were prescribed for 3 days. However, these drugs did not induce an additional decrease in PAP. The patient was extubated after removal of the Swan Ganz catheter on the sixth postoperative day. The last checked systolic PAP was 65 mmHg with mPAP of 47 mmHg. Treatment with oral sildenafil 25 mg was continued until the next follow-up day. Postoperative echocardiography demonstrated minor improvement, with an ejection fraction of 66%, RVSP of 54 mmHg, and mPAP of 33 mmHg. At this time, 4 months after the LT, there have been no

complications related to PHT and we decided to continue on treatment with oral sildenafil.

## Discussion

In the case of severe PPHT, with mean PAP over 45 mmHg and PVR over 240 dyne·sec/cm<sup>5</sup>, some clinicians do not recommend LT [1]. A previous study has revealed an intraoperative mortality rate of up to 50% [5]. In patients with severe PPHT, the response to preoperative pulmonary vasodilators plays an important role in the prognosis after liver transplantation [6]. So, if use of these vasodilators does not show preoperative decrease in PPHT, we have to consider whether proceeding with liver transplantation is appropriate, because it is difficult to predict the postoperative prognosis. However, nearly 50% of patients with severe PPHT, who showed a response to vasodilator therapy, had no change in the long-term outcome [4]. There is little evidence to guide decision-making on whether to proceed with LT in the presence of severe PPHT. The reasons we proceeded with the surgery even though the patient showed severe PPHT (systolic PAP, 107 mmHg; mPAP, 68 mmHg; PVR, 788 dyne·sec/cm<sup>5</sup>; and PCWP, 14 mmHg, measured immediately after anesthesia) were as follows. First, there were no symptoms and signs related to preoperative PHT. This could be explained by the patient being tolerant of that degree of PHT. This indicated that she would be able to tolerate the surgery if the PHT did not increase much more intraoperatively. With the use of many different types of pulmonary vasodilators, vasomodulators, volume restriction, and limited use of vasopressors, there was no additional increase in PAP. Second, after anesthetic induction, severe PPHT responded to 200 µg of nitroglycerin bolus, and mPAP was decreased from 68 to 50 mmHg. This meant that PPHT had responded to the drugs, and we could predict satisfactory results with pulmonary vasodilators such as inhaled iloprost and milrinone and pulmonary vasomodulators. Third, although the preoperative ascites was very severe, we expected the PPHT to possibly be relieved by drainage of ascites. This could mean that severe ascites compressed the lung base in the supine position. It functioned as a factor associated with rise in pressure and resistance of intrapulmonary vasculature. In fact, after about 9,000 ml of ascitic fluid was drained in this case, the mPAP decreased from 62 to 42 mmHg, CVP from 12 to 9 mmHg, and PVR from 533 to 394.5 dyne·sec/cm<sup>5</sup>.

Several methods are available for management of severe PPHT. Previous studies have indicated that early use of milrinone [2], long term use of phosphodiesterase 5 inhibitors such as sildenafil [7], inhaled nitric oxide, and prostanoids such as

inhaled iloprost [8] improve oxygenation and alleviate PPHT without any hepatic hemodynamic changes [9,10]. From the preoperative to postoperative period, we used all the drugs mentioned above. Though these drugs prevented additional increase in PAP, they did not show a dramatic normalization of PAP. We attribute this to the fact that the vascular wall may have already undergone a conformational change due to the pathophysiologic mechanism. A continual increase in the portal hypertension may have caused structural change of the pulmonary vasculature in the form of abnormal proliferation of vascular smooth muscle and pulmonary capillary endothelial cells, infiltration of the inflammatory cells, and fibrosis [6].

We focused not only on medical interventions to lower PAP, but also on the anesthetic management by minimizing electrolyte imbalance, delicate management of the fluid balance, and restriction of vasopressor use. Generally, in the reperfusion phase, increased venous return affects right ventricle function by volume overload, which may lead to right heart failure [11]. To reduce this complication, we tried to minimize intraoperative blood loss, and subsequently the amount of volume therapy and transfusion were minimal with a consensus between the surgeons and anesthesiologists before the surgery. As the use of a vasopressor in the periods of occasional hypotension might result in an additional increase in PAP by its effect on pulmonary vasculature, we did not use any vasopressors that could influence SVR and PVR during the entire duration of the surgery. We were able to control intermittent intraoperative hypotension and low CO with milrinone and low dose dobutamine for preventing further increase in PAP. We maintained end-tidal CO<sub>2</sub> at a low level between 25 and 30 mmHg for pulmonary vasodilation. Because of the above-mentioned efforts, the reperfusion syndrome was transient, and the amount of blood loss and transfusion was minimal, which in turn contributed to the maintenance of hemodynamics. We were able to maintain the PAP within the expected range even in the presence of surgical stresses. We would not have had this result if we had relied on medical interventions alone. At this time, the patient is alive and in good condition, without any complications related to PPHT.

In conclusion, in a patient with severe PPHT, who is to undergo LT, a successful transplantation is not guaranteed if we depend only on pulmonary vasodilators or vasomodulators. To achieve better outcome, thorough management such as ensuring minimal blood loss and transfusion, meticulous volume control, maintenance of low end-tidal CO<sub>2</sub>, and restriction of vasopressors, beside from administration of pulmonary vasodilating agents, also required.

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