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Epidemiology and Clinical Management of Pulmonary Hypertension in Children

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Pulmonary hypertension (PH) is a clinical hemodynamic syndrome characterized by increased pulmonary artery pressure and pulmonary vascular resistance. It can cause right ventricular failure, and even death. Pediatric PH is not very common, but is a greatly hazardous disease that leads to a high mortality rate. Therefore, many registry organizations have been established in the world to strengthen the study of diagnosis and treatment of the disease, and improve the understanding of pediatric PH. This article reviewed recently published researches, as well as presented a comprehensive understanding of PH, including definition, classification, epidemiology, prognosis and treatment. **(Korean Circ J 2012;42:513–518)**

KEY WORDS: Hypertension, pulmonary; Incidence; Disease management; Child.

Introduction

Pulmonary hypertension (PH) is a clinical hemodynamic syndrome characterized by increased pulmonary artery pressure and pulmonary vascular resistance (PVR). It can cause right ventricular failure, and even death. Pediatric PH is a rare disease, but is a greatly hazardous disease, which leads to a high mortality rate. Therefore, a number of studies for the registry of the disease have been conducted in the world, including the Registry to Evaluate Early and Long-Term pulmonary arterial hypertension (PAH) Disease Management (REVEAL) and the Tracking Outcomes and Practices in Pediatric Pulmonary Hypertension (TOPP),[1-6] to strengthen the study of diagnosis and treatment of the disease. Multi-center studies on the incidence, diagnosis, treatment and prognosis of pediatric PH were published recently, which greatly improved the understanding of pediatric PH. Despite such improvement, there has not been pediatric PH epidemiological data in China.[7]

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Definition and Classification of Pediatric Pulmonary Hypertension

The commonly used definition of PH is that at the sea level, in the resting state, the mean pulmonary artery pressure (mPAP) is ≥25 mm Hg, pulmonary capillary wedge pressure is normal (≤15 mm Hg) and PVR increases, developed in the Fourth Global Meeting of PH held in 2008 in Dana Point, United States.[8] Whether or not the definition applies to pediatric patients, especially to infant patients, is controversial. Experts suggest that the ratio of the systolic pulmonary artery pressure to the systolic systemic blood pressure >0.4 should be the diagnostic criterion. In addition, the threshold of PVR increase has not been set in the abovementioned definition which is unsuitable for pediatric patients, since pediatric PH is mainly caused by left-to-right shunt congenital heart diseases; and if PVR shows no significant increase in such cases, the patient may be considered only as a dynamic PAH led by increased pulmonary blood flow, rather than pulmonary vascular disease. Therefore, almost all pediatric PH specialists suggest that PV >3 Wood units remain in the definition of pediatric PH.[9]

According to the latest Dana Point classification, PH is divided into five categories: 1) PAH, including idiopathic or familial (IPAH or FPAH), PAH associated with connective tissue disease, congenital systemic to pulmonary shunts, portal hypertension, HIV infection, drugs and toxins and others, as well as PAH associated with significant venous or capillary involvement, such as pulmonary venous-occlusive disease and pulmonary capillary hemangiomatosis, and persistent

pulmonary hypertension of the newborn (PPHN); 2) PH with left heart disease; 3) PH associated with lung diseases and/or hypoxemia; 4) PH due to chronic thrombotic and/or embolic diseases; and 5) PH caused by miscellaneous.[8] Whether or not the classification is applicable to pediatrics is also controversial. For example, common diseases, such as bronchial dysplasia and congenital diaphragmatic hernia, which cause pediatric PH, have not been included in any classification.[9] In addition, TOPP studies show that many PH children have comorbid disorders (24%), such as trisomy 21 combining with left-to-right shunt congenital heart disease and PH, but the presence of congenital heart disease are not in accordance with the severity of PH. Whether this kind of children is attributed to be diagnosed with PAH associated with congenital systemic to pulmonary shunts or FPAH is controversial.[5] As such, pediatricians suggested a 10 item-based classification suitable to pediatric PH recently, but it has not yet been widely applied.[10]

Epidemiology and Prognosis of Pediatric Pulmonary Hypertension

The publication of the above registered study report on pediatric PH provides a more clear understanding of epidemiological characteristics of pediatric PH. In the United Kingdom and New Zealand, incidences of IPAH are 0.48/1000000 and 0.7/1000000, respectively. Prevalence rates are 2.1/1000000 and 4.4/1000000, respectively.[2)4] In New Zealand, the incidence of PAH associated with congenital systemic to pulmonary shunts is 2.2/1000000, and the prevalence rate is 15.6/1000000. Registry studies in New Zealand indicated that the most common transient PHs in children were PPHN and pre-operative PAH associated with congenital systemic to pulmonary shunts, and incidence is 30.1/1000000 and 21.9/1000000,[4] respectively. The most common diseases in children with persistent PH are IPAH and PAH associated with congenital systemic to pulmonary shunts. A number of studies have found that IPAH/FPAH shows the highest proportion in these children (35-60%), and PAH associated with congenital systemic to pulmonary shunts accounts for about 24-52%.[1–6] With the significantly increased number of survived premature children, most specialists considered that PH, caused by bronchopulmonary dysplasia (BPD), might have been underestimated in most studies. The TOPP and the Swiss studies revealed that BPD accounted for 12-13% in PH children.[5] On the gender ratio, studies in adults revealed that the incidence of PH in females was significantly higher than that of males, and the female/male ratio was 4/1, while in pediatric patients with PH, the proportion is much lower, female/male ratio being 2/1.[5)6]

The most common symptom of pediatric PH is exertional dyspnea, which is presented in 53-66% of children with IPAH/FPAH, and about 30-60% of children with PAH associated with congenital systemic to pulmonary shunts. Syncope is the second most common symptom in pediatric PH, but it mainly appears in children with IPAH/FPAH. While only 4% of children with PAH associated with congenital systemic to pulmonary shunts present syncope. Unlike adult PH patients, though the pulmonary artery pressure of pediatric patients has also been high when symptoms appear, symptoms of right ventricular failure, such as edema presented in PH children are far less than those presented in PH adults. Therefore, most PH children are diagnosed as grade I-II, by World Health Organization (WHO) functional classification. Results of the 6-minute walking test conducted on PH children beyond 7 years old are often normal.[9)10]

If no targeted treatment is conducted on patients with PH, they would show a very poor prognosis. For example, in adult patients with IPAH/FPAH, the average time from diagnosis to death is 2.8 years, and in children with IPAH/FPAH, the prognosis might be worse. It is reported that only 37% of IPAH/FPAH children without targeted treatment survive within one year after the diagnosis; and no patients can survive for 7 years.[5)9] However, in recent decades, the discovery and clinical application of a series of targeted drugs for the treatment of PH have greatly improved the prognosis of patients with PH. Though most drugs are supplied for adult patients, and no indications of children can be found in these instructions, these drugs beyond instructions for use have also significantly improved the prognosis of pediatric patients with PH. According to the report of the REVEAL study, the average 5-year survival rate of all PH children, including those with IPAH/FPAH and PAH associated with congenital systemic to pulmonary shunts was 74%.[6] Haworth and Hislop[2] also reported 1 year, 3-year and 5-year survival rates of a group of IPAH children after receiving single-agent or combination therapy, including intravenous epoprostenol, bosentan or sildenafil, were 86%, 80% and 72%, respectively. Similar conclusions were also drawn in the registration study in France and the study in the United States.[3)11]

Treatment of Pediatric Pulmonary Hypertension

Since information on randomized controlled studies on the treatment of pediatric PH is very limited, presently, unanimous opinions are to refer to the guidelines and treatment strategies for the treatment of adult PH. Therefore, the recommended treatment for children is only grade IIa with the level of evidence class C.[9]

Right heart catheterization is very important for the initial treatment of pediatric PH, because it can not only diagnose some diseases, such as pulmonary vein disease in addition to PH, but also help to understand acute pulmonary vasodilator responses in pediatric patients, which is very important to decide whether the cal-

cium channel blocker (CCB) treatment can be used for children. Presently, a variety of quick-acting vasodilator drugs can be used for acute pulmonary vasodilator test internationally, including inhaled nitric oxide, intravenous epoprostenol and intravenous adenosine. Traditional positive response criteria are as follows. After the test, the mPAP decreases by greater than 20%, cardiac output increases or is at least unchanged.[12] However, the specificity of the standard is very low, so the more stringent positive-response criteria is used for adults as follows. The mPAP decreases by more than 10 mm Hg and the absolute value is ≤40 mm Hg, cardiac output increases or is at least unchanged. But whether or not the standard is applicable to pediatric patients remains unclear. In REVEAL and TOPP registry studies, positive standards of the test and the long-term efficacy after the application of CCB are observed. It can be seen from results of the present study that the younger the patient, the higher the positive rate. Positive response rate of children with PAH is about 11-40%, while that of adults is about 6-27%.[9][12]

Comprehensive treatment

Diuretics can reduce the excessive volume load in patients with right ventricular dysfunction; digoxin can increase cardiac output, is effective to right ventricular dysfunction and can decrease cardiac output-related PH, but present clinical experience is rare. Hypoxia may cause pulmonary vasoconstriction to aggravate PH. So, oxygen inhalation therapy can be conducted on patients whose arterial oxygen concentration is below 90%, in particular, on those who have paroxysmal nocturnal dyspnea. But whether or not an oxygen therapy is suitable for Eisenmenger syndrome is still controversial. Anticoagulant is mainly used for IPAH children. Due to its micro-thrombosis mechanism, it can also be used for right ventricular dysfunction, or for patients who have undergone long-term intravenous drug therapy. Warfarin and aspirin are commonly used. The risk/benefit ratio should be assessed in long-term use. Young children are recommended to be treated with aspirin, since it is more difficult to control the suitable international normalized ratio for young children using warfarin. In addition, a rational use of sedatives can prevent the occurrence of PH crisis.[13] It is suggested that PH children should be routinely inoculated with influenza virus vaccines to prevent an upper respiratory tract infection, because it can aggravate alveolar hypoxia in children. Drugs containing pseudoephedrine should be avoided to be used for upper respiratory infection.

Calcium channel blockers

Currently, large doses of CCB have been advocated as the first-line oral therapeutic drug for PH patients who show positive results in acute vasodilator test. However, there has been no report on the randomized controlled clinical studies. Though the positive rate of an acute pulmonary vasodilator response in pediatric PH patients is higher than that in adult PH patients, the majority of PH children (about 70-90%) show negative results in acute vasodilator test. Therefore, other targeted drugs of PH are still needed for the majority of PH children.[9][10][13][14]

Prostacyclins

Epoprostenol is an intravenous preparation of prostacyclin first used clinically. It has been used for the treatment of PH patients in the early 1980s. In a prospective randomized open trial, 81 patients with severe IPAH (grade III-IV by NYHA functional classification) were randomly divided into the conventional treatment group (anticoagulant, diuretics, oxygen therapy, oral vasodilators), and conventional treatment combining with the epoprostenol treatment group. The results showed that in the prostacyclin treatment group, the mPAP and the mean PVR were decreased, and thus, the mortality was decreased. Yung et al. confirmed the long-term efficacy of intravenous epoprostenol in children with IPAH and PAH associated with other diseases, and 61% of children receiving the treatment of the drug were still alive after 10 years of application. Epoprostenol has been approved for the treatment of PH patients in Europe and North America in the mid-1990s.[9][10][13-15]

Epoprostenol has a short half-life (2-5 minutes). Therefore, it needs to be used by continuous intravenous drip. Major adverse reactions include facial flushing, headache, jaw pain, leg pain, diarrhea, nausea, intravenous infection and thrombosis.[9][10][13-15]

The clinical application of epoprostenol is limited because of its special specifications. Therefore, a series of prostacyclin derivatives have developed in recent years. Representative drugs include the following:

1) Treprostinil: it is a stable analogue of PGI_2, which can be administered intravenously or subcutaneously. The injection solution has been come into the market in the United States in 2002 for the treatment of PH. In 2002, Simonneau et al.[16] reported a multi-center randomized double-blind controlled clinical trial and confirmed that both pulmonary artery pressure and cardiac output were significantly improved in the treatment group of subcutaneous treprostinil, and the progress of exercise tolerance depends on the drug dose. The major adverse reaction of the subcutaneous injection of prostacyclin was the injection site pain (appear in 85% of patients). But, its applications are particularly limited in pediatric patients. However, a recent study on the subcutaneous application of treprostinil in pediatric PH patients indicated that the drug was well tolerated in children. There have been reports on the treatment of pediatric PH by treprostinil inhalation.[17]

2) Iloprost: it is a chemically stable prostacyclin analogue. With a long half-life, it can be used as a substitute for epoprostenol. Rou-

tes of administration include intravenous, inhalation and oral administration. In the present studies, the most widely used is iloprost inhalation. Iloprost inhalation has been approved by the Food and Drug Administration (FDA) in the United States, and also for patients diagnosed with IPAH (grade III) in Europe. Lately, 12 weeks of randomized double-blind placebo-controlled multi-center clinical trial was conducted in Europe. The study showed that in the iloprost inhalation treatment group, hemodynamics, including pulmonary artery pressure and cardiac output, were significantly improved, as well as cardiac function classification, quality of life and dyspnea indexes. Its disadvantages include the short duration of action and syncope which is commonly seen in the treatment group. Recently, Ivy et al.[18] reported the short and long-term efficacy of iloprost inhalation in the treatment of PH in children; they treated 22 cases of 5 to 18-year-old children (12 patients with IPAH, 10 patients with congenital heart disease and PH) by the inhalation of 2.5-7.5 μg of iloprost, 5 to 9 times per day. They found that iloprost inhalation might be an effective treatment for only a part of the children with PH. 35% of patients showed improved WHO cardiac function classification, 50% showed no change, and 15% of patients showed decreased WHO cardiac function classification. Most children who accept long-term inhalation therapy can stop the long-term intravenous injection of prostaglandin.

Endothelin receptor antagonists

Bosentan (bosentan) is an oral non-selective endothelin receptor antagonist, with the dual antagonism of ETA and ETB. In 2001, Channick et al.[19] carried out a bosentan multi-center, randomized double-blind, placebo-controlled study on the treatment of PH for the first time. Later on, at least six randomized studies on the bosentan treatment of PH caused by various factors were conducted. The diseases include IPAH, scleroderma-associated PH, PAH with congenital heart disease and Eisenmenger's syndrome. Results showed that bosentan could persistently improve the quality of life of patients with PH. It is a new effective drug to treat patients with PH.[9-14]

There are some reports on bosentan treatment in pediatric PH. In 2003, bosentan has been used in treating pediatric PH (BREATHE-3 study), and its pharmacokinetics and safety were evaluated. In this study, bosentan doses used were 31.25 mg bid in children weighing 10 to 20 kg, 62.5 mg bid in children weighing 20 to 40 kg and 125 mg bid in children weighing >40 kg. According to 19 children with PH diagnosed as grade II and III, by WHO cardiac function classification (IPAH or PAH-associated congenital systemic to pulmonary shunts), the study first confirmed that the pharmacokinetics of bosentan in pediatric PH was similar to that in adult PH. It could significantly improve the hemodynamics, and safely be used in the treatment of pediatric PH.[9)11)13)14)] Simpson et al.[20] conducted a fol-

low-up study on seven children with IPAH, who received bosentan treatment (single administration or with sildenafil/warfarin/epoprostenol) in 2001, and they found that 3- and 5-year survival rates of patients after bosentan treatment were 100% and 75% respectively, significantly higher than those in the control group (33% and 33%). A retrospective study of 86 PH children revealed that after 14 months of bosentan treatment alone or in combination with other drugs, clinical and hemodynamic parameters of children showed continuous improvement, and the 2-year survival rate was up to 91%. They continued to conduct the follow-up visit of these children for four years, and predicted the survival rate to be 82%.[11] In another study on 101 children with IPAH and PAH associated with congenital systemic to pulmonary shunts treated with bosentan, 1-, 2-, 3- and 5-year survival rates were 96%, 89%, 83% and 60%, respectively.[21] Bosentan could also be used in patients with Eisenmenger syndrome, and the randomized placebo controlled study revealed that bosentan could improve the exercise activity of patients with the disease, and increase peripheral oxygen saturation. There have been reports on the efficacy of bosentan treatment in children with PAH associated with congenital systemic to pulmonary shunts, indicating that after bosentan treatment, the mPAP of children was decreased and heart function improved. In addition, no significant adverse reactions appeared.[22] However, studies indicated that the long-term efficacy of bosentan treatment could not be maintained in children with severe PH.[23]

The side effect of bosentan is mainly liver dysfunction. The risk of liver dysfunction in children is lower than that in adults. The incidence of adult patients is about 10%, while that of children is about 3%.[24] In addition, the efficacy of the selective ETA receptor antagonist ambrisentan in treatment of PH in adult patients has been recognized.[9)10)14)] A small number of reports on pediatric PH patients also showed that the application of bosentan treatment in some children changed to the application of ambrisentan treatment, and children conditions were further mitigated.[10]

Phosphodiesterase type 5 inhibitors

Sildenafil is a selective phosphodiesterase type 5 (PDF5) inhibitor. It increases the intracellular cyclic guanosine monophosphate (cGMP) levels by inhibiting the degradation of cGMP, causing vascular smooth muscle relaxation and pulmonary vascular dilatation. It can also enhance and extend the effect of vascular dilatation of NO and PGI2, as well as its analogues. In a multi-center randomized double-blinded, placebo-controlled study, a total of 278 patients with symptomatic PAH were enrolled. The study found that sildenafil significantly improved the exercise tolerance, hemodynamics and WHO functional classification of patients.[9)10)13)14)] It was reported that 25 infants with PH secondary to chronic lung disease, includ-

ing 18 children with BPD, were treated with sildenafil. Further, a series of echocardiographic follow-up visits showed that conditions of the majority of children (88%) with PH were improved. In addition, these children had no obvious adverse reactions.[25] Recently, a 16-week randomized double-blinded test verified the efficacy of sildenafil in pediatric PH patients. A total of 235 PH children, aged from 1 to 17 years old, were treated with a low-dose, medium-dose and high-dose sildenafil or placebo. The results showed that compared with the placebo, medium-dose and high-dose of sildenafil significantly improved the maximum oxygen consumption, the mPAP, PVR and cardiac function of children, while no effects were shown in the low dose group. Further observation of the low doses, moderate doses and large doses of sildenafil used in children and the Kaplan-Meier curve analysis showed that all 1-year survival rates of these children were 100%, 2-year survival rates 95%, 95% and 92% for low doses, moderate doses and large doses of sildenafil treatment, respectively, and 3-year survival rates were 92%, 90% and 84%, respectively. The deaths of children were related to the causes and severity of diseases. The majority of children who died had IPAH/FPAH, and their mPAP, PVR and right atrial pressure were relatively high.[26] In Europe, sildenafil has been approved to be used in pediatric PH patients. The dosage was as follows: for children over 20 kg, 10 mg, 3 times/day, and for children >20 kg, 20 mg, 3 times/day. Sildenafil can also be administered intravenously. A recent study showed that the application of intravenous sildenafil in PPHN could significantly improve the oxygenation index of children. Sildenafil could be well tolerated, and the most common side effect was headache.[10][13]

Tadalafi is another selective PDF5 inhibitor. Its duration of action is longer than that of sildenafil. It has been approved by the U.S. FDA for the treatment of patients with PH in 2009. A recent study revealed that tadalafil taken once daily could improve the medication compliance of PH children and have effects as sildenafil.[10]

Since the incidence of PH involves a variety of ways, many researchers conducted drug combination by one, two or three ways to relieve clinical symptoms and improve patients' prognosis. Even very limited experience is obtained for empirical combination therapy of pediatric PH presently.[14][27]

Surgical treatment of pediatric pulmonary hypertension

Lung transplantation or heart-lung transplantation is a last chance for patients with PH who underwent ineffective medical treatment. The atrial septal incision can be used as a transitional means of pre-transplant in patients with refractory right heart failure. Atrial septal incision is another alternative treatment for patients infeasible to transplantation. Patients received lung transplantation, without complications can live a normal life, restore normal or near nor-

mal activities and have good prospects for long-term survival.[13][14]

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