Combination Therapy of Prostacyclin for Pulmonary Hypertension in Congenital Heart Disease

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Background: *Pulmonary arterial hypertension (PAH) is a recognized complication of congenital heart disease. Despite differences in etiology and pathophysiology, successful therapy for idiopathic PAH may benefit in patients with congenital heart disease. We theorized that combination of oral and aerosolization prostacyclin will benefit this group of patients in long term.*

Material and Method: *The study design was single group and open label study with intention to treat for patients with congenital heart disease with pulmonary artery (PA pressure) more than 50% of systemic pressure. All patients were given a combination of orally given beraprost sodium and inhalation of iloprost for 12 months. Data were collected prospectively consisting of functional class, O_2 saturation, 6-minute walk test and right ventricular systolic pressure (RVSP).*

Results: *There were 23 patients with an average right ventricular systolic pressure ($\pm$ SD) of 94.8 $\pm$ 14.5 mmHg and with average age of 27.8 $\pm$ 14.9 years (2.5 to 50 years). The average oxygen saturation was 87.9 $\pm$ 7 %. There were 12 patients with post surgical repair or cardiac catheterization interventional procedure and 11 with and Eisenmenger's syndrome. There were significant improvement of 6-minute-walk test from an average of 268 $\pm$ 70 meters to 308 $\pm$ 57 meters at the end of 12 months. The functional class of patients was also improving. However, there were no significant different in oxygen saturation.*

Conclusion: *Combination therapy of oral and inhalation of aerosolized vasodilators is a fascinating concept in the therapy of pulmonary hypertension. Treated patients showed an improvement in exercise capacity and right ventricular systolic pressure without a worsening in oxygen saturation.*

Keywords: *Pulmonary hypertension, Congenital heart disease*

J Med Assoc Thai 2005; 88(Suppl 8): S60-5
Full text. e-Journal: *http://www.medassocthai.org/journal*

Most patients with pulmonary hypertension with significant clinical symptoms were encountered in children and adults with congenital heart disease[1-2]. These patients had secondary pulmonary artery hypertension (PAH) from significant left to right shunt. Treatment strategies for pulmonary hypertension in patients with congenital heart disease vary with acuity or chronicity of the hypertensive disorder. Underlying causes of pulmonary hypertension may arise secondary to congenital heart diseases or associated with repair or palliation of structural heart diseases. It could also be associated with some degree of idiopathic or primary PAH[3]. Recently the WHO classified idiopathic PAH and secondary PAH from congenital heart disease into the same category to emphasize the common basis of pathobiology[4]. Traditional therapy for IPAH in adults has been applied to children and adults with congenital heart disease primarily as an extension of adult recommendations[5]. Few rigorous clinical studies are available to provide the basis for this practice. Nonetheless,

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recent extensive clinical experience and general medical consensus suggested an important role for selective pulmonary vasodilator therapy[6].

Multiple publications have shown that any of the medications or perhaps a combination effect of prostacyclin (oral, inhalation or intravenously), phosphodiesterase inhibitor (as an endogenous nitric oxide precursor), or endothelin receptor antagonists could improve the conditions in this group of patients[7-12]. In general, these medications have several side effects if used in full dose as in IPAH. Recent publications encouraged a combination of medications in patients who did not respond well to either one of the medications[13-14]. In Thailand, two preparations of prostacyclin analogs were approved for treating of pulmonary hypertension; orally given of beraprost sodium (BPS)[2] and inhalation of iloprost. BPS as a monotherapy was reported to be effective in patients with mild to moderate degree of PAH (New York Heart Association (NYHA) class I or II)[10]. However, since the majority of our patients had pulmonary artery pressure more than 50% of systemic pressure and were in New York Heart Association (NYHA) class III and IV, we theorized that a combination therapy may overcome this limitation.

Our objectives were to determine whether combination therapy with prostacyclin analog is effective for severe PAH in congenital heart diseases.

Material and Method

We enrolled patients with PAH from congenital heart defect including those with Eisenmenger's syndrome (right to left shunt) creating pulmonary hypertension. The study was an open label, single group with intention to treat in all patients. The combination of treatment was considered in patients with severe PAH defined as the ratio of pulmonary artery pressure to systemic blood pressure is more than 0.5. All demographic data were recorded. All patients were treated with both beraprost sodium (initial dose of 1 mcg/kg/day up to maximum dose of 4 mcg/kg/day) and inhalation of iloprost (initial dose of 20 mcg/day up to maximum of 80 mcg/day) given in two to three separated doses. All patients were followed for oxygen saturation, functional class and 6-minute-walk test (performed in patients who were older than 5 years old)[15] at premedication (premed), 3 months, 6 months, 9 months and 12 months. Echocardiogram was performed at premed, 6 months and 12 months for right ventricular systolic pressure (RVSP)[16]. All side effects and additional laboratory (complete blood count and liver function test) were recorded at the begining and at the end of follow-up period. The study on chronic therapy on BPS was approved by ethical committee from the Faculty of Medicine Siriraj Hospital.

Statistical analysis

The 6-minute-walk test, oxygen saturation and right ventricular systolic pressure were the primary efficacy outcome parameter. Other laboratory values at the end of 12 months were compared to baselines per protocol by using the students unpaired t-test. Data were reported as mean with standard deviation (mean $\pm$ SD). A significant change was defined as $p < 0.05$ (two-tailed). If the data at 12 months were not available because of termination of the treatment for other reasons, the last data between 8 and 12 months were adopted for analysis. The missing values for other measurements were excluded from the analysis.

Results

There were 23 patients with severe PAH with average RVSP of 94.8 $\pm$ 14.5 mmHg and their average age was 27.8 $\pm$ 14.9 years (2.5 to 50 years). The average oxygen saturation was 87.9 $\pm$ 7 %. Their diagnoses were 10 atrial septal defects (ASD), 3 ventricular septal defects (VSD), 2 patent ductus arteriosus (PDA) and 8 complex congenital heart diseases. Their treatments staging were post surgical repair or cardiac catheterization interventional procedure in 12 patients and Eisenmenger s syndrome in 11 patients. The dosage and follow-up results were shown in Table 1. There were few side effects including headache and dizziness in 6 patients during the first month of medication. After BPS was slowly up titrated dosage, these symptoms appeared to be attenuated. The only side effects noted is the redness and flushing of the faces which occurred in the area exposed to inhalation (perioral area).

6-minute-walk test and Functional class (Table 1 and Fig. 1)

There were 20 patients who were older than 5 years old and were able to complete 6-minute-walk at the end of 12 months period. There were significant improvement of 6-minute-walk test from an average of 268 $\pm$ 70 meters to 308 $\pm$ 57 meters. Although at the beginning of 9 months there appeared to be a dropping in 6-minute-walk test to 292 $\pm$ 69 meters, however, there were only 3 patients who had deterioration in 6-minute-walk test. The rest of the patients had an improvement in their 6-minute-walk test. The average

increased in 6-minute-walk of 71 ± 86 meters was noted from premedication to the end of 12 months. At the beginning of the study, there were 1 patient in NYHA class I, 17 in class II and 5 in class III. After 12 months of treatment, there was an improvement in functional class with 7 patients in class I, 15 patients in class II and only one patient in class III (Fig. 1). There were only two hospitalizations for congestive heart failure symptoms. Both patients were treated with iloprost inhalation and low dose milrinone for few days.

Right ventricular systolic pressure and oxygen saturation

The average right ventricular systolic pressure (RVSP) before treatment was 86 ± 22 mmHg and decreased to 70 ± 22 mmHg and 72 ± 24 mmHg at 6 month and 12 months, respectively ($p < 0.001$). The improvement in RVSP appeared to be leveled off at the end of 6 months. The oxygen saturation was maintained during 12 months of therapy. They appeared to be no worsening in oxygen saturation after 12 months of combination therapy.

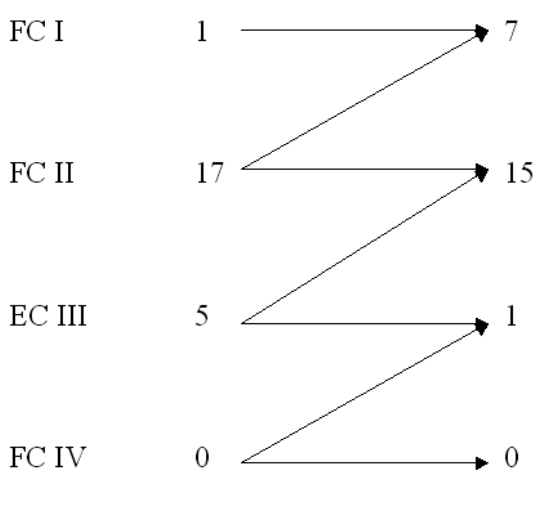

Fig 1. Changing of New York Heart Association (NYHA) functional class (FC) before and at the end of 12months treatment. There was no deterioration of functional class at the end of 12 months

Discussion

Severe pulmonary hypertension is a life-threatening disease characterized by an increase in pulmonary artery pressure and pulmonary vascular resistance. In general, this group of patients had a potential to develop right ventricular failure and decrease functional class[16]. In our study, we defined severe pulmonary hypertension as the ratio of pulmonary to systemic pressure of more than 0.5. There were 23 patients with majority of them were in NYHA class II or III. The average 6-minute-walk was 268 ± 70 meters which was below normal population (300 meters and up)[15,17,18]. In the past, these groups of patients were treated with supportive management such as diuretics and afterload reduction therapy. The underlying pathophysiological mechanisms of this disease comprise remodeling processes, *in situ* thrombosis, and persistent vasoconstriction of blood vessels in the pulmonary circulation. An imbalance in the synthesis of vasoconstrictive (thromboxane, endothelin) and vasodilator agents (EDRF, prostacyclin) seems to play an important role in the etiology of pulmonary hypertension[19-20]. This pathophysiological background offers the possibility of developing treatment strategies, including application of vasodilator drugs such as prostacyclin analog.

In a recent approach to overcome some of the hazards inherent in systemic vasodilator therapy, aerosolization of vasodilator agents was employed for pulmonary vasodilation in both primary and severe secondary pulmonary hypertension[14,21]. In the very first clinical studies with aerosolized prostacyclin (PGI2) in patients suffering from acute pulmonary hypertension due to pneumonia or ARDS, a selective vasorelaxation in the pulmonary circulation was

Table 1. The results of treatment in patients with combination of beraprost and iloprost at premedication (premed), mo (months), 6 min walk = 6-minute-walk test, RVSP = right ventricular systolic pressure (mmHg), Sp O_2 = Oxygen saturation

	Premed	3 mo	6 mo	9 mo	12 mo	p-value
6 min walk(meters)	268 ± 70	317 ± 49	318 ± 64	292 ± 69	308 ± 57	< 0.001
RVSP (mmHg)	86 ± 22	-	70 ± 22	-	72 ± 24	< 0.001
Sp O_2 (%)	93 ± 5.6	91.5 ± 8.2	93.5 ± 6.8	92.6 ± 7.2	91.3 ± 8.4	NS
BPS dosage (mcg/day)	67 ± 30	72 ± 31	72 ± 27	64 ± 27	54 ± 19	
Iloprost dosage(mcg/day)	21 ± 17	23 ± 17	27 ± 21	26 ± 22	27 ± 22	

achieved with a maximum pulmonary vasodilatory potency corresponding to that of intravenous prostacyclin[14,22]. The preferential distribution of aerosolized prostacyclin to well-ventilated lung areas improved ventilation-perfusion matching and shunt flow. Prostacyclin, however, has a very limited biological half-life of only 2-3 minutes. In contrast, the stable prostacyclin analogue-iloprost has a longer half-life and shows identical biological effects and efficacy profile. We intended to use the combination of two types of prostacyclin analogs to overcome the short half-life effect of each type of prostacyclin. In general, patients take oral beraprost sodium 3 to 4 times daily, in addition to three times daily of inhalation of iloprost instead of 6-9 times of inhalation as originally described for iloprost monotherapy[21]. This combination was intended to exert the maximum effect of each prostacyclin and to diminish the intensity of inhalation which could result in long term acceptance of the patients and more financially sound in developing countries.

The combination of therapy in our study had an average increased in 6-minute-walk of 71 $\pm$ 86 meters which is well over a landmark study[21]. In that study with idiopathic pulmonary hypertension after 3 months of inhalation with monotherapy (iloprost), the benefit was shown as increasing in 6-minute-walk test of only 36 meters. We believed that patients with congenital heart diseases and left to right shunt were known to have better long term prognosis due to preserved right ventricular function from systolic decompression of the defect[16]. There was no significant difference in improving of 6- minute-walk test after 12 months between patients with Eisenmenger's or post-operative patients. All patients including those in the Eisenmenger's group were able to maintain their oxygen saturation during 12 months.

Conclusion

Combination therapy of oral and inhalation of aerosolized vasodilators is a fascinating concept in the therapy of pulmonary hypertension, providing selectivity of the hemodynamic effects to the lung vasculature and reducing systemic side effects. This combination of prostacyclin analogs both orally and inhalation not only improved the 6- minute-walk test but also minimized side-effects and was financial suitable for long term therapy in patients with pulmonary hypertension without worsening the oxygen saturation.

Grants support

Study was supported by Cardiac Surgery Foundation of Thailand.

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การรักษาผู้ป่วยโรคหัวใจพิการแต่กำเนิดที่มีความดันหลอดเลือดแดงในปอดสูงด้วยยาพอสต้า-ไซคลินสองชนิด

กฤตย์วิกรม ดุรงค์พิศิษฏ์กุล, เดโช จักราพานิชกุล, ดวงมณี เลาหประสิทธิพร, จารุพิมพ์ สูงสว่าง, ประคัลภ์ จันทร์ทอง, อภิชาติ นานา

ภาวะความดันหลอดเลือดแดงในปอดสูงพบได้บ่อยในผู้ป่วยโรคหัวใจพิการแต่กำเนิด ซึ่งผู้ป่วยเหล่านี้สามารถให้การรักษาได้เหมือนกับผู้ป่วยที่มีภาวะความดันหลอดเลือดแดงในปอดสูงชนิดไม่ทราบสาเหตุ

วัสดุและวิธีการ และผลการศึกษา: *การศึกษานี้เป็นการใช้ยาพรอสต้าไซคลินสองชนิดคือ ชนิดรับประทาน (beraprost sodium) และชนิดสูดดม (iloprost) ร่วมกันในผู้ป่วยโรคหัวใจพิการแต่กำเนิดที่มีภาวะความดัน หลอดเลือดแดงในปอดสูงโดยที่มีความดันในหลอดเลือดแดงของปอดอย่างน้อย 50% ของ systemic pressure เป็นเวลา 12 เดือน โดยตรวจติดตามพบว่า ผู้ป่วยมีการออกกำลังที่ดีขึ้นโดยค่า 6-minute-walk เพิ่มจาก 268 $\pm$ 70 เมตร เป็น 308 $\pm$ 57 เมตร และมี ค่าความดันในช่องหัวใจล่างข้างขวาลดลงโดยที่ไม่มีการเปลี่ยนแปลงของค่าความอิ่มตัว ของออกซิเจน*

สรุป: *การใช้ยาพรอสต้าไซคลินสองชนิดทำให้ผู้ป่วยโรคหัวใจพิการแต่กำเนิดที่มีความดันหลอดเลือดแดงในปอดสูงอย่างรุนแรงมีอาการดีขึ้นจากการออกกำลังกายได้มากขึ้นและมีความดันในช่องหัวใจล่างข้างขวาที่ลดลง*