

## Oral Sildenafil for pulmonary hypertension associated with congenital heart disease in children – single center, prospective, pilot study

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### Abstract

**Objective:** To study the efficacy of oral sildenafil for pulmonary hypertension (PH) in children associated with congenital heart disease.

**Methods:** This was a prospective observational study carried at Neonatal and Pediatric Intensive Care Unit of tertiary care hospital for a period of 1 year. Fifty children with pulmonary hypertension associated with congenital heart disease were given Sildenafil at a dose of 1mg/kg /dose 6 hourly either oral or through nasogastric tube & were followed up for a period of six months clinically & with serial echocardiography.

**Results:** Pulmonary hypertension was observed more in female (64%) patients. Majority (88%) of children had moderate to severe pulmonary hypertension. All children were malnourished. Cardiomegaly (92%), Respiratory distress (76%), congestive cardiac failure (76%), Anemia (84%) & pneumonia (52%) were common clinical presentations in these children. Mean pulmonary pressure at admission was 62.92±17.48 mm of Hg. There was significant (p-0.00) reduction in serial pulmonary pressures (at 2 weeks 51.71±19.06, at 1 month 48.42±21.55, at 3 month 37.92±20.85 and at 6 month 29.27±14.40mm of Hg). Sildenafil has reduced the pulmonary pressures in all grades of pulmonary Hypertension. Episodes of congestive cardiac failure and pneumonia were reduced after sildenafil treatment. Sildenafil was tolerated well in patients of all grades of pulmonary hypertension with a very few side effects like diarrhea (10%), flushing(8%) and tachycardia (6%).

**Conclusion:** Sildenafil which is easily available, inexpensive & well tolerated drug not only reduces pulmonary pressures in patients of all grades pulmonary hypertension but also reduces episodes of congestive cardiac failure and pneumonia.

**Keywords:** Sildenafil, Pulmonary Hypertension, Critically ill children, PICU.

### Introduction

Pulmonary hypertension of any origin may be associated with significant morbidity and mortality. Regardless of origin, it can be progressive and severe and can lead to right ventricular failure, arrhythmias, and death. Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest.<sup>(1)</sup> There is elevation in the pulmonary artery pressure in the congenital heart disease which is caused by pulmonary overcirculation, pulmonary vasoconstriction, and pulmonary vascular disease. Mechanisms of the disease include pulmonary endothelial dysfunction, leading to impaired production of vasodilators, such as nitric oxide and prostacyclin and overexpression of vasoconstrictors, such as endothelin-1, prostacyclin and thromboxanes. Approximately one third patients with uncorrected congenital heart disease will die from pulmonary vascular disease. When surgical repair is performed in presence of high PVR and hypoxemia, it is associated with high post-operative mortality.<sup>(1,2)</sup>

Treatment of pulmonary hypertension includes conventional agents like anticoagulants, diuretics, digoxin, and supplemental oxygen, as well as calcium channel blockers in selected patients, intravenous epoprostenol, the inhaled prostacyclin analogue iloprost, the subcutaneously and intravenously administered prostacyclin analogue treprostinil, and the oral

endothelin-receptor antagonist bosentan. Although these drugs are efficacious, adverse effects in terms of safety, tolerability, drug delivery or all of these factors occur with all of these agents. Inhaled NO is used to reduce PH but some patients fail to respond to nitric oxide inhalation.<sup>(2,3)</sup>

While responders to long term no therapy may develop severe, life-threatening, rebound pulmonary hypertension on withdrawal of nitric oxide. These are expensive options for resource limited setting.<sup>(4)</sup> Sildenafil a vasodilator is administered orally, is well tolerated with few drug interactions, and does not require intensive monitoring, making it an attractive alternative to other drugs for the treatment of PH.<sup>(5)</sup> We narrate our experience of using an inexpensive pulmonary vasodilator, sildenafil, a phosphodiesterase inhibitor, in pulmonary hypertension associated with CHD in children.

### Aims and Objectives

To study the clinical presentation of pulmonary hypertension (PH) in children with congenital heart disease and to study the efficacy of oral sildenafil for pulmonary hypertension in children with congenital heart disease.

## Material and Methods

The present study was prospective observational pilot study carried out at department of pediatrics of a tertiary care hospital over a period of one year from Jan 2015 to Dec 2015. Fifty cases with Congenital heart disease in whom Pulmonary Hypertension was detected on Echocardiography were included. Detail history and physical examination in every case was carried out. Initial 2D-echocardiography (ECHO) was done at the time of first visit. PH was detected by using velocity time integral (VTI) in relation to tricuspid regurgitation. Depending upon the pulmonary pressures detected on 2D-ECHO on first visit, cases in the present study were classified under 3 grades.<sup>(6)</sup> Mild PH (25–45 mmHg), Moderate PH (45–60 mmHg) & Severe PH (more than 60mmHg). All cases had received sildenafil at a dose of 1mg/kg /dose 6 hourly either oral or through nasogastric tube and followed up to a period of 6 months. Repeat ECHO study was done at 2 weeks, 1 month, 3 months and then after 6 months of interval. Changes in pulmonary artery pressures were recorded in each case. Simultaneously clinical status of congenital heart disease and adverse effects of sildenafil were also recorded over a period of time. Other investigations like complete blood count, chest x-ray, arterial blood gas analysis were carried out in all patient and as indicated. The data were presented as mean  $\pm$ Standard deviation. Normally distributed continuous variables were compared with Student's t-test and categorical variables were compared with Chi-square test or Fisher's exact test. Non-Normally Distributed Data was compared with Mann-Whitney test and Kruskal-Wallis test. Repeated pulmonary pressure measurement were studied as longitudinal data analysis using Linear mixed models. In all comparisons, P value <0.05 was considered significant. IBM SPSS software 19.0 was used for statistical analysis.

## Results

Out of 50 cases in study group 20 were neonates and 26 were infants, two were between age of 2 years to 5 years and two were above 5 yrs. Median age was 2 months (range - 1month to 12 years) Majority (64%) of cases were females. Forty two (84%) patients were

anemic, eight (16%) patients had metabolic acidosis and 6(12%) had sepsis. Forty six (92%) had cardiomegaly, out of which 14(30 %) had hyperemic lung fields on X-ray. 2DECHO findings at study entry revealed twelve patient with isolated ASD, four with isolated VSD and two with isolated PDA .While ASD+VSD combination in eighteen cases, ASD+PDA in six cases, VSD+PDA in two cases and ASD+VSD+PDA noticed in six cases. Only six cases (12%) had mild PH while rest 44(88%) had moderate & severe pulmonary hypertension 22 cases each. Eighteen patient had respiratory distress, eight had hypoxemia while twelve patients were asymptomatic at admission. As per Indian Academy of Pediatrics classification of protein energy malnutrition, twelve patients had grade I, eighteen patient had grade II, fourteen patient had grade III and six patient had grade IV malnutrition. Out of six cases with mild PH, one had pneumonia. While amongst twenty two cases with moderate PH twelve cases congestive cardiac failure and fourteen had pneumonia. Out of twenty two cases with severe PH all had congestive cardiac failure & sixteen cases had pneumonia on admission. After receiving oral or nasogastric Sildenafil (at dose of 1mg/kg/dose at six hourly) all 50 case were followed up. Two were operated before 3 months; while two were operated after 3 months and two patients died after 3 months. Mean pulmonary pressure at admission was  $62.92 \pm 17.48$  Hg, at 2 weeks  $51.71 \pm 19.06$ , at 1 month  $48.42 \pm 21.55$ , at 3 month  $37.92 \pm 20.85$  and at 6 month  $29.27 \pm 14.40$  mm of Hg. This was significant reduction ( $p=0.00$ ) in serial pulmonary pressure. (Fig. 1) Sildenafil has reduced the pulmonary pressures in all grades of pulmonary Hypertension. (Table 1) Episodes of congestive cardiac failure and pneumonia were reduced after sildenafil treatment. The pulmonary pressures were normalized in 26 patients, pulmonary pressure not normalized but reduced in 18 patients while only 6 patients in which pulmonary pressure not reduced. (Table 2) Sildenafil was tolerated well in patients of all grades of pulmonary hypertension with a very few side effects like diarrhea (10%), flushing(8%) and tachycardia (6%). Follow up ECHO revealed reduction of ASD size in 30 patient, reduction of VSD size in 10 patients, reduction in PDA in 2 patients.

**Table 1: Pulmonary arterial pressures at different stages of follow up**

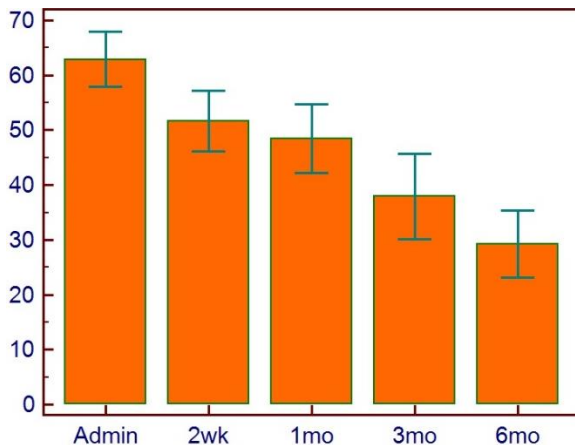
	Admission	At 2weeks	At 1 month	At 3 months	At 6 months
Mild PH (N=6)	40 $\pm$ 5	47.5 $\pm$ 10	34 $\pm$ 5.9	22 $\pm$ 2	22.33 $\pm$ 4.04
Moderate PH(N=22)	55.18 $\pm$ 5.19	44.72 $\pm$ 6.08	43.36 $\pm$ 15.98	38.45 $\pm$ 23.83	31.27 $\pm$ 32.8
Severe PH (N=22)	77.81 $\pm$ 15.32	65.81 $\pm$ 17.20	59.50 $\pm$ 20	36.4 $\pm$ 11.17	41.62 $\pm$ 27.91

**Table 2: Changes in pulmonary hypertension**

	Total N=50	Mild PH N=6	Moderate PH N=22	Severe PH N=22
Pulmonary pressure normalized	26	4	16	6
Pulmonary pressure reduced	18	2	4	12
Pulmonary pressure not reduced	6	0	2	4

**Table 3: Side effects of sildenafil**

	Total N=50	Mild PH N=6	Moderate PH N=22	Severe PH N=22
Diarrhea	5	1	2	2
Flushing	4	1	1	2
Tachycardia	3	0	1	2



**Fig. 1: Changes in Pulmonary pressures in study period**

**Discussion**

Over the past decade, there has been a significant advance in the treatment of PH. Intravenous and inhaled prostanoids, nitric oxide and endothelin inhibition show promise. Inhaled nitric oxide is the most selective pulmonary vasodilator and has been used successfully in PH of varied origin. Prostaglandin therapy has been instituted by using epoprostenol as a continuous infusion.<sup>(7)</sup> Aerosolised formulation like iloprost has been used successfully in patients with PH after repair of the CHD. Bosentan –a non-selective endothelin inhibitor – is available for oral administration. Follow up data over three years have shown few deteriorations, with majority of patients maintaining their response on bosentan alone.<sup>(8)</sup> However, bosentan therapy is costly, US \$ 10,000 per year for an adult. Sildenafil, a phosphodiesterase type-5 inhibitor, is a selective pulmonary vasodilator. It is well tolerated and is available as an oral preparation.<sup>(9)</sup>

Beneficial Effect of Injetable Sildenafil Therapy on Childhood Pulmonary Arterial Hypertension have been studied in large number of studies.<sup>(10-14)</sup> There is limited international data available about oral sildenafil therapy for pulmonary hypertension secondary to congenital heart disease and so also from India.<sup>(15-17)</sup> Higher incidence of pulmonary hypertension in females in our study is consistent prior studies.<sup>(3,8)</sup> Children with pulmonary hypertension presented with poor appetite, failure to thrive, lethargy, diaphoresis,tachypnea, tachycardia and irritability. Most of the children in our study group had grade 2 to grade 3 protein energy malnutrition. Respiratory distress and Hypoxemia were main presenting features seen during the study period. These clinical features in our study were consistent with prior studies.<sup>(1,2,3,8)</sup>

In present study we have used sildenafil at dose of 1mg/kg/day every 6 hourly, similar dose was used in most of the previous studies.<sup>(15-18)</sup> We have observed that sildenafil has significantly reduced pulmonary artery pressures (PAP) in majority of cases with pulmonary hypertension in all grades of severity. After sildenafil was started the episodes of CCF and pneumonia were reduced but the upper respiratory tract infection remain persistent. These finding were consistent with published data.<sup>(15-18)</sup> Sildenafil was well tolerated in all patients with different age groups and with different severity of pulmonary hypertensions. Minor side effects like diarrhea, flushing or tachycardia in very small number of subjects.

We found usefulness of sildenafil, as inexpensive pulmonary vasodilator, in pulmonary hypertension associated with CHD in children. Sildenafil can be given orally very easily and in a sick baby through nasogastric tube. Sildenafil is easily available. Sildenafil 50 mg tablet costs only Rs 12. Thus for a 5 kg child it will cost just Rs.140 for one month medication which is very negligible compare to other available modalities to treat pulmonary hypertension. Sildenafil has very less or no side effects. Sildenafil tolerance is very well without a withdrawal effect. Thus we can recommend the use of sildenafil in patient with PH associated with CHD.

The limitations of our study can be attributed to: The small number of patients, the absence of randomization and the lack of a contemporary control group. Confirmation of these promising findings in a randomized, controlled clinical trial is essential to verify efficacy, tolerance and safety.

**Conclusion**

Sildenafil which is easily available, inexpensive & well tolerated drug not only reduces pulmonary pressures in patients of all grades of pulmonary hypertension but also reduces episodes of congestive cardiac failure and pneumonia.

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