

**ROLE OF SILDENAFIL IN MANAGEMENT OF POST-OPERATIVE PULMONARY HYPERTENSION IN CHILDREN.**

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**ABSTRACT**

**Objective:** To evaluate the effectiveness of oral sildenafil on post-operative pulmonary hypertension in children following surgery for congenital heart disease. **Study design:** Retrospective Analytical study **Patients and Methods:** Fifty four consecutive patients between 2005 and 2013 with congenital heart defects (ventricular septal defects and patent ductus arteriosus) with systemic or supra systemic pulmonary artery pressures post operatively were included in the study. In all these patients sildenafil was given post operatively and the Ratio of pulmonary artery pressures to systemic pressures was recorded and presented as a percentage. These pressures were recorded at 0, 1, 6, 12 and at 24 hours intervals. After discharge pulmonary artery pressures were calculated by transthoracic echocardiography at 3 and 6 months and at one year. **Results:** The age of patients ranged from 1 to 28 years (mean of  $7.2 \pm 6.1$  years) and 53.7% (n=29) were male. The mean PA pressures were  $90.52 \pm 17.19$  percent of aortic pressures pre-operatively, which dropped to  $57.94 (+/- 12.60)$  percent of aortic pressures after 24 hours ( $p < 0.001$ ) with sildenafil therapy. A further decrease in pulmonary artery pressures was seen at 3 months ( $42.29 +/- 13.59$ ) percent of aortic pressures, at 6 months ( $34.23 +/- 14.60$ ) percent of aortic pressures. After 1 year the PA pressures were  $31.17 (+/- 15.42)$  percent of aortic pressures. **Conclusion:** Oral sildenafil is readily available and effective as an adjunctive agent in the treatment of post operative pulmonary hypertension.

**KEYWORDS:** Pulmonary Hypertension, Sildenafil, Congenital Heart Disease, Ventricular Septal Defect, Patent Ductus Arteriosus.

**INTRODUCTION**

Pulmonary arterial hypertension (PAH) secondary to congenital heart defects is one of the most difficult disease to treat postoperatively. The child with post operative pulmonary hypertension remains a therapeutic challenge. There have been marked improvements in survival over the decade for some forms of PAH. The treatment options have expanded in recent years, but medications used to induce pulmonary vasodilation and/or cause regression of remodeling within the pulmonary vascular bed have had limited success due to lack of efficacy, nonselectivity, cost, adverse effects, and complications.<sup>[1]</sup>

Various therapeutic options including intravenous epoprostenol<sup>[2]</sup> inhaled iloprost<sup>[3]</sup> endothelin receptor blockers<sup>[4]</sup> inhaled NO<sup>[5]</sup> and phosphodiesterase inhibitors<sup>[6]</sup> have become available in recent years with varying degrees of success. However most of them remain unavailable in the third world for a variety of

reasons. Surgical closure of ventricular septal defects (VSD) in children with high pulmonary vascular resistance (PVR) carries a significant risk of post operative morbidity and mortality primarily due to intermittent pulmonary hypertensive crisis and compromised cardiac output. Since PVR worsens overtime, the risk of surgical complications increases with advancing age.<sup>[7,8]</sup> Utilization of unidirectional fenestrated double flap valve patch for closure of VSD's has resulted in low peri-operative mortality.<sup>[9]</sup> However after VSD closure some patients have persistent pulmonary hypertension and would benefit from pulmonary vasodilation. Traditional therapy with intravenous and inhaled pulmonary vasodilators has limited availability and logistic barriers to their use in under developed countries. Late diagnosis in Pakistan leads to severe forms of PAH which pose greater post op problems. We report our use of oral sildenafil as an adjunctive agent for the treatment of post-operative

pulmonary hypertension in children undergoing repair of VSD's.

### MATERIALS AND METHODS

The pediatric cardiac surgical database of AFIC/NIHD was reviewed for all patients undergoing VSD closure between December 2005 and December 2011. All patients who had pulmonary artery pressures equal to or more than 50% of systemic pressures after VSD closure were given sildenafil for the treatment of PAH. The VSD type was peri-membranous in 46 patients, peri-membranous additional muscular VSD in 5 patients, one patient had peri-membranous VSD with patent ductus arteriosus (PDA), one patient had double outlet right ventricle (DORV) with subaortic VSD and one patient had an isolated large PDA. All patients had pulmonary hypertension on pre-operative catheterization. 7/54 patients were identified who had previously been placed on sildenafil following cardiac catheterization.

### Anesthetic and Operative Care

All patients received a percutaneously inserted pulmonary artery pressure measuring line prior to sternotomy. Routine bi-caval cannulation and cardiopulmonary bypass were employed and the operations performed at 34°C. The VSD was closed using the flap valve double patch technique in all patients. Immediately following release of the cross-clamp a loading dose of milrinone (50 mcg/kg) was given intravenously. Sildenafil (2 mg/kg) was given at this time as well via a nasogastric tube. Dopamine (2-10 mcg/kg/min) and epinephrine (0.03-0.1 mcg/kg/min) were used as indicated.

### Intensive Care Unit

Patients were transferred to the PCICU following surgery and allowed to awaken from anesthesia in all cases regardless of the pulmonary artery pressure. Extubation was performed when the respiratory parameters were satisfactory. Pulmonary artery pressures did not routinely guide plans for extubation. Sildenafil administration was continued in the PCICU at an initial dose of 1 mg/kg/dose every six hours. If there was not a response to the initial dose of sildenafil the subsequent dose was 2 mg/kg. Systemic arterial and pulmonary artery invasive pressures were measured continuously. The arterial blood gas and echo-cardiogram were obtained if patients desaturated to determine if shunting across the fenestration was occurring in a right to left manner. Milrinone was generally tapered off as captopril was added, whereas dopamine and epinephrine were discontinued as clinically indicated. Pulmonary artery pressure lines were maintained for a minimum of 24 hours.

### Hospital Discharge

Patients were discharged on sildenafil at doses ranging from 1-2 mg/kg/dose. Sildenafil dosing was every 6 hours. A discharge echocardiogram was obtained to assess the velocity of the tricuspid regurgitant jet as a

measure of peak systolic pulmonary artery pressure and the pulmonary valve regurgitant jet as an indicator of diastolic pulmonary artery pressure. Sildenafil was continued for a maximum of 3 months except in four patients in which it was continued for a year and echocardiographic follow-up was obtained at 3 month intervals for 1 year.

### Data Analysis

All values are expressed as the mean  $\pm$  standard deviation. Comparison of pulmonary artery pressures was performed using the student's t-test and P values less than 0.05 were considered significant.

### RESULTS

The age of patients ranged from 1 to 28 years, with a mean of  $7.2 \pm 6.1$  years. The preoperative PAP/AoP pressure ratio was  $90.5\% \pm 17.2$ , the mean PVR was  $10.3 \pm 4.2$  Wood units and the mean Qp/Qs was  $1.5 \pm 0.39$ . The PAP/AoP ratio fell to  $86.5\% \pm 15.1$  with oxygen provocation, and the PVR fell to  $7.7 \pm 2.9$  Wood units and the Qp/Qs increased to  $2.2 \pm 0.5$ . The ratio of PAP/AoP following MUF was  $75.9 \pm 21.03\%$  of systemic and differed significantly from those obtained pre-operatively ( $P < 0.01$ ). The ratio of PAP/AoP in the 7 patients on sildenafil preoperatively was  $97.85 \pm 9.06\%$  of systemic and differed from the post bypass values,  $77.57 \pm 21.82\%$  of systemic (table 1 & 2). Mean cardiopulmonary bypass time was  $78.4 \pm 33.3$  minutes and mean cross-clamp time was  $49.5 \pm 25.5$  minutes.

### PCICU Care

All patients were transferred to the ICU intubated on 100% FiO<sub>2</sub>. The mean extubation time was  $7.6 \pm 8.2$  hours with a range of 1.5-48 hours. Intermittent pulmonary hypertensive crises were observed in 72% (N=39/54). The flap valve double patch prevented the patients from severe hemodynamic compromise secondary to providing right to left shunting thereby maintaining cardiac output. Systemic desaturation did occur with a range of 75 to 95%. No patient died of these pulmonary hypertensive episodes. The pulmonary hypertensive episodes were mainly observed during the extubation process. Two patients who were in the pre operative Sildenafil group experienced three of these pulmonary hypertensive episodes each.

Pleural effusions occurred in 9 patients and required furosemide and digoxin for resolution, suggesting right ventricular dysfunction. Hospital mortality was 3.7% (2/54) secondary to sepsis.

**Follow-Up:** 52 patients were discharged on sildenafil on a dose that ranged from 1-2 mg/kg/dose. Sildenafil was continued in all patients for the first three months in all patients. 44 patients had their sildenafil discontinued at this time. The mean PAP/AoP ratio for those in whom the sildenafil was discontinued was  $37 \pm 7.89\%$  and in those in whom it was continued was  $68.75 \pm 8.57$  ( $P < 0.01$ ). The mean PAP/AoP ratios for 3, 6 and 12 months

post-discharge were shown on table 3. The value at each time period in follow-up was significantly lower than pre-op ( $P < 0.01$ ). Four patients in the sub group of 7 that received sildenafil pre operatively died after 1 year. Cause of death was not known as all four died at home.

**Table. 1 Pre Operative Data of Sub Group of 7 Patients With Very Severe PHT**

PVR(mean) on air	PVR(mean) on O2	Mean PAP/AoP %
15.7±0.57	12.57±1.255	98.75±2.5
13.46±0.5	10.06±1.1	93.33±11.54
P=0.005	P=.227	P=0.423

**Table.2 Patients on Pre op Sildenafil In Sub Group of 7 Patients**

Mean PAP/AoP Post Op %	Mean PAP/AoP 24 Hours %	Mean PAP/AoP 3 Months %	Mean PAP/AoP 6 Months %	Mean PAP/AoP 1 Year %	Mean Extubation time	Mean ICU stay
92.5±9.57	73.75±2.5	68.75±8.57	67.5±8.66	62.5±2.88	4.62±2.42	3.5±1.29
73.33±23.09	48.33±2.88	43.33±7.63	35±5	23.33±2.88	6±1	5±5.19
P=0.225	P=0.013	P=0.051	P=0.04	P=0.001	P=0.465	P=0.625

**Table 3: Paired correlations of pre bypass PAP/ AoP to Post bypass PAP/AoP at different time intervals.**

PRE BYPASS PAP/AoP	90.529±17.19	P<0.01
POST BYPASS PAP/AoP	75.0±21.03	
PRE BYPASS PAP/AoP	90.529±17.19	P<0.01
PAP/AoP AT 24 HOURS	57.94±12.68	
PRE BYPASS PAP/AoP	90.529±17.19	P<0.01
PAP/AoP AT 3 MONTHS	42.294±13.59	
PRE BYPASS PAP/AoP	90.529±17.19	P<0.01
PAP/AoP AT 6 MONTHS	34.23±14.60	
PRE BYPASS PAP/AoP	90.529±17.19	P<0.01
PAP/AoP AT 1 YEAR	31.17±15.42	

## DISCUSSION

The effect of Sildenafil on pulmonary vasculature has been the focus of several recent clinical trials which are briefly discussed. The description of the use of oral sildenafil for treating pulmonary hypertension secondary to congenital heart defects or paediatric cardiac surgery is limited only to case reports, nonrandomized studies and small randomized trials. Stocker et al, in a prospective randomized trial of 16 ventilated infants early after closure of ventricular septal defect and atrioventricular septal defect reported significant reduction in pulmonary vascular resistance index when sildenafil was used in conjunction with inhaled nitric oxide. Sildenafil reduced the SVR and systemic blood pressure and worsened arterial oxygenation and alveolar arterial gradient.<sup>[10]</sup> Schulze-Neick et al, in a prospective non randomized trial demonstrated that intravenous Sildenafil is more effective in reducing the PVR than nitric oxide.<sup>[11]</sup> Atz et al, showed that sildenafil augments the effect of inhaled nitric oxide in postoperative pulmonary hypertensive crisis and suggested a role of sildenafil during the phase of weaning nitric oxide.<sup>[13]</sup>

Kothari et al reported the outcome of chronic oral sildenafil therapy in five patients who had surgery for congenital heart disease.<sup>[14]</sup> Improvement in NYHA functional class, six minute walk test and pulmonary artery pressures was witnessed. Farah Peiravian et al, in a prospective randomized study investigated the role of oral Sildenafil in decreasing pulmonary pressures after congenital heart surgery. Postoperative PA pressure (28.61± 7.80 vs 39.40 ± 10.80 mmHg) and PA/Ao pressure (0.28 ± 0.08 vs 0.41± 0.11) were significantly lower in Sildenafil group ( $p = 0.001$  and  $0.001$  respectively).<sup>[15]</sup>

There is a two pronged challenge to treat post operative pulmonary hypertension in the the third world. Firstly most cases with advanced and severe pulmonary hypertension are encountered whereas developed nations don't see such patient population. Secondly most of the latest treatment options are not available in the third world. In our study comprising 54 patients the most severe forms of pulmonary hypertension were encountered. This can be gauged by the fact that all

patients had pre-operative systemic or supra systemic pulmonary artery pressures and only those patients were included in the study whose pulmonary artery pressures were more than half systemic after corrective surgery. The reason for such severity is probably late diagnosis as can be seen from mean age at surgery ( $7.2 \pm 6.14$  years). Sildenafil was incrementally increased and increasing the dose did help in decreasing the PA pressures without significant side effects. Common side effects included penile erections in male patients, visual disturbances and severe myalgias when dose was increased to 3 mg/kg in two patients after which no patient received a dose exceeding 2 mg/kg. In the sub group of seven patients that received pre operatively the mean PAP/AoP were comparable pre operatively and immediately after coming off bypass. However in the survivor group the PAP/AoP were significantly lower after 24 hours and continued to decline. Lately as Bosentan and oral Beraprost became available in Pakistan, we did try them as combined therapy with sildenafil. Their combination with sildenafil caused profound bleeding from mucosal surfaces, after which their use in combination was abandoned.

## CONCLUSION

Sildenafil can be considered a safe drug for post-operative pulmonary hypertension especially in third world countries where there are still logistic and economical barriers to more selective and expansive drugs. This study was carried out before the FDA med alert that increasing dose of sildenafil for pulmonary hypertension increases mortality. It is worth mentioning that we continue to see that sildenafil decreases pulmonary artery pressures in the post operative period.

## Study Approval

The Ethics Committee at AFIC/NIHD reviewed and approved the study Informed consent was obtained from the parents and or patients prior to surgery.

## Study limitations

This study was not a randomized study as we didn't want to deprive these children of the only hope at reducing PA pressures.

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