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Sildenafil Use in Children with Pulmonary Hypertension.

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Abstract

Objective: To assess the demographics, treatment algorithm and outcomes in a large cohort of children treated with sildenafil.

Study design: A retrospective cohort study of children with pulmonary hypertension (PH) treated with sildenafil at a single institution between 2004-2015. Baseline and follow up data collected by chart review.

Results: 269 children with idiopathic PAH (IPAH) (n=47), congenital heart disease (CHD) (n=53), bronchopulmonary dysplasia (BPD) (n=135), congenital diaphragmatic hernia (CDH) (n=24), and other (n=7). Sildenafil was initial monotherapy in 84.8%, add-on therapy in 15.2%. Median follow-up time was 3.1 years (2wks-12.4y). On follow up, 99 (37%) remained on sildenafil or transitioned to tadalafil, 93 (35%) stopped sildenafil for improvement in PH, 54 (20%) died, and 20 (7%) were lost to follow-up. PH was most likely to improve in BPD, allowing discontinuation of sildenafil in 45%. Eighteen deaths were related to PH, and 36 from other systemic causes. Two patients stopped sildenafil due to airway spasm with desaturation. Overall survival was significantly lower in WHO Group 3 PH (BPD and CDH) vs Group 1 (IPAH and CHD), $P = .02$.

Conclusion: In this retrospective experience in children with mainly WHO group 1 and 3 PH, low dose sildenafil was well tolerated, safe and with an acceptable side effect profile. Although patients with group 3 PH have high mortality, survivors have a high likelihood of PH improving.

Keywords

Sildenafil; bronchopulmonary dysplasia; congenital diaphragmatic hernia; congenital heart disease

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death.¹⁻⁴ Sildenafil is a

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phosphodiesterase (PDE) type 5 inhibitor approved for treatment of pulmonary arterial hypertension (PAH) in adults. PDE-5 inhibitors have vasodilatory effects in the pulmonary vasculature via an increase in cyclic guanosine monophosphate (cGMP).⁵⁻⁶ Sildenafil is not currently Federal Drug Administration (FDA) approved in the pediatric population, however it has been extensively used off-label for pediatric PH since 2005, mostly based on adult studies as there are limited pediatric data.⁷⁻¹¹

The “Sildenafil in Treatment-Naïve Children, Aged 1-17 Years with Pulmonary Arterial Hypertension” (STARTS-1) trial, a 16-week randomized, double blind placebo-controlled study, examined the effects of oral sildenafil monotherapy in pediatric patients with PAH, including idiopathic pulmonary arterial hypertension (IPAH), and PAH associated with connective tissue disease (CTD) and congenital heart disease (CHD). Peak oxygen consumption, mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance indexed (PVRI) improved with the medium and high dose sildenafil, and there was no significant change with low dose sildenafil.¹² In the long term extension study (STARTS-2) there was increased mortality noted at three years associated with high dose sildenafil in children with IPAH, but not in children with PAH associated with CHD.¹³ Review of these data by the FDA and European Medicines Agency (EMA) resulted in contradictory recommendations; sildenafil was approved by the EMA in 2011 with a later warning on avoidance of the use of high dose sildenafil, and the FDA released a black box warning against the use of sildenafil in pediatric patients aged 1-17. The Pediatric Pulmonary Hypertension Network (PPHNet) put forth a consensus statement highlighting the limitations of the START-2 extension study and the FDA warning was later revised to add that health care providers should consider the risk and benefits of sildenafil for the individual patient.¹⁴⁻¹⁶

Given the controversy and limited data on treatment of pediatric pulmonary hypertension with sildenafil, our aim was to describe our large single center experience with the use of sildenafil in infants and children with pulmonary hypertension.

Methods:

This is a retrospective cohort study of 269 pediatric patients with pulmonary hypertension (< 18yo) who initiated treatment with sildenafil between December 1, 2004 and December 31, 2015 with or without pre-existing targeted PH therapy. Patients were excluded if the patient had group 2 PH including cardiomyopathy, and those with single ventricle physiology. Baseline and follow-up data were collected retrospectively from medical charts; end of data collection was Dec 31, 2016 giving an at least 1 year follow up period for patients on sildenafil.

Addition of other PH-specific therapy was recorded. Survival status and treatments were assessed for all patients at the end of data collection, regardless of whether sildenafil was continued or discontinued. Events leading to discontinuation were collected to understand reasons for stopping and side effects.

Statistical analyses were performed using Stata software, version 14.0 (StatCorp, College Station, Texas). Clinical variables were described using standard summary statistics including median with range for non-parametric data. Mann-Whitney test, chi-squared test, and log rank test were used to compare medians, proportions, and mortality, respectively. A p-value of <0.05 was considered statistically significant. This study was approved by the Columbia University Medical Center's Institutional Review Board.

Results:

There were 269 patients who met inclusion criteria (134 male, 135 female). Forty-seven patients (17%) had IPAH, 53 patients (20%) had PH associated with CHD, 3 (1%) had PH associated with CTD, 135 patients (50%) had PH associated with bronchopulmonary dysplasia (BPD), and 24 (9%) had PH associated with congenital diaphragmatic hernia (CDH). Seven patients were classified as "other". Three of these patients had glycogen storage diseases, two had mucopolysaccharidosis Type 1 (Hurler Syndrome), and two had skeletal abnormalities with associated restrictive lung disease.

The median age at pulmonary hypertension diagnosis was 6 months (1 week-16.3 years) and the median age at sildenafil initiation was 7 months (1 week-17.1 years). Median follow-up time after sildenafil initiation was 3.1 years (2 weeks-12.4 years) (Table I). The maintenance dosing range for all patients was 1mg/kg/dose given enterally every 8 hours. There were 5 patients early in the study period transferred to our institution on sildenafil every 6 hours, but were changed to every 8 hour dosing during the hospitalization as soon as possible. Patients were not discharged on every 6 hour dosing. If parenteral dosing was needed, the dose was 50% of the enteral dose. As shown in Table 2, the majority of patients (84.8%) started sildenafil as monotherapy, 38 patients (14.1%) started sildenafil as add-on therapy, and 3 patients (1.1%) started sildenafil concurrently with other PH specific medications. Thirty-nine percent of patients required an additional medication added to sildenafil, with a median time to additional medication of 6 months (1week-10.5 years). As an institutional protocol, patients with WHO functional class III or IV symptoms were started on a continuous prostanoid infusion as first line therapy for pulmonary hypertension, and those patients in functional class I or II were usually started on sildenafil as first line therapy. Most patients with IPAH had a cardiac catheterization prior to initiation of pulmonary vasodilator therapy (43/47, 93%). About two-thirds of patients with CHD had a catheterization prior to initiation of sildenafil (33/53, 62.3%). It was rare for patients with PH associated with BPD to have a cardiac catheterization prior to sildenafil initiation, often due to the small patient size and patient fragility, with only 20/135 (14.8%) of infants undergoing cardiac catheterization prior to sildenafil initiation. Similarly patients with CDH and PH rarely had cardiac catheterization prior to sildenafil initiation (2/24, 8.3%). If BPD and CDH patients were not able to be weaned off sildenafil within one year, then a cardiac catheterization was performed to assess pulmonary artery pressure, evaluate intra or extracardiac shunting, rule out pulmonary vein stenosis and evaluate for left ventricular diastolic dysfunction. Patients with IPAH had follow up cardiac catheterizations every 1-3 years, with the frequency determined by clinical status and changes in therapy.

Outcomes at the end of data collection were assessed (Table 3). 33% of patients continued on sildenafil, 4% transitioned to tadalafil, and 35% discontinued sildenafil due to improvement in PH. For patients who were able to stop sildenafil due to improvement in PH, the median time of sildenafil use was 1.7 years (2 weeks-8.6 years). Two patients with BPD discontinued sildenafil due to side effects, specifically desaturations due to airway spasm. No patient stopped sildenafil due to a perceived lack of efficacy. There were no patients that had to decrease sildenafil dose due to other side effects, however some patients with priapism underwent a slower uptitration of the sildenafil dose. One patient received a lung transplant, 20% (n=54) died, with 18 of 54 deaths related to PH, and the remaining 36 deaths were thought to be due to respiratory failure or an infectious etiology. Sildenafil had been stopped in one patient prior to death some weeks later, and the remaining patients died while on sildenafil. Seven percent of patients were lost to follow-up. The overall survival starting from sildenafil initiation is shown in the Kaplan Meier curve in the Figure, comparing survival of WHO Group 1 PH (IPAH, CHD and CTD) and Group 3 PH (BPD and CDH). The 1, 3, and 5 year survival after sildenafil initiation overall was 90%, 86%, and 84% respectively. In group 1 patients the 1,3, and 5 year survival after sildenafil initiation was 98%, 94%, and 90% respectively. In group 3 patients the 1,3, and 5 year survival after sildenafil initiation was 84%, 80%, and 78% respectively. Survival was significantly worse in group 3 PH vs. group 1 PH ($p=0.02$) and mortality was mainly related to systemic complications of prematurity and BPD. There was no difference in survival in the inpatients initially treated with sildenafil every six hours compared with those treated every 8 hours, although this was a very small sample size.

Patients with IPAH were significantly older at PH diagnosis and sildenafil initiation, and had a longer follow-up time compared with the remainder of the cohort (Table 1). These patients were much more likely to require addition of another PH specific medication, with 83% of patients requiring additional medication (83% vs. 43%, $p<0.001$). Twenty-four patients needed one additional medication during the follow-up period, and 15 patients required 2 additional medications. Median time to additional medication was 7 months (2 weeks-8.8 years). Five of the patients who were started on sildenafil as add-on therapy to epoprostenol were eventually able to have epoprostenol weaned off. Four of five of these patients were started on an oral endothelin antagonist in addition to sildenafil.¹⁷ Patients with IPAH were more likely to continue on a PDE 5 inhibitor (sildenafil or tadalafil) throughout the follow-up period, compared with the remainder of the cohort (77% vs. 33%, $p<0.001$). As expected, no patients with IPAH discontinued sildenafil due to improvement in PH.

Patients with PAH associated with congenital heart disease had a median age at PH diagnosis of 10 months (1month-15.8 years), with median age at sildenafil initiation of 1.2 years. Most patients (92.5%) started sildenafil as first line PH therapy. Nineteen patients (36%) required additional medication added, with a median time to additional medication of 1.1 years (2 weeks-10.5 years). This time to additional medication was significantly longer than the remainder of the cohort (1.1 years vs. 6 months, $p<0.01$). Fifteen patients had one medication added, and 4 patients received 2 additional medications. There were 3 patients on continuous systemic therapy with epoprostenol or treprostinil, 2 of whom died from pulmonary hypertension during the study period, and the other is currently undergoing evaluation for a lung transplant. About half of the patients (49%) were still on a PDE 5

inhibitor at last follow-up. 36% were weaned off sildenafil for improvement in PH with a median time on sildenafil of 1.1yrs (1mo-7.5yrs). Type of CHD and whether they were repaired is shown in Table 4 (available at www.jpeds.com). The most common type of CHD in this cohort was atrioventricular (AV) canal defect (22 of 57 patients). Patients with unrepaired shunts on sildenafil were deemed candidates for repair when their PVRi was less than 6 Wood units*m² and the ratio of pulmonary to systemic resistance less than 0.33.

There were 29 patients in our cohort with trisomy 21. The majority (n=18) of these patients had PAH associated with CHD (15 atrioventricular canals, 2 ventricular septal defects and 1 patent ductus arteriosus). Of these patients, six had unrepaired shunts when started on sildenafil, and four of six subsequently underwent successful repair of the shunt. The remainder (n=12) were patients with PAH after shunts were repaired. There were four patients with IPAH with no associated congenital heart disease or significant lung disease. Seven patients had PAH associated with BPD and all of these infants were premature with gestational age ranging from 28-32 weeks with significant lung disease. Two of these BPD patients had minor congenital heart disease (one with a small atrial septal defect and one with a small patent ductus arteriosus). Outcomes for these patients are shown in Table 5 (available at www.jpeds.com) with about one-half of patients on sildenafil or tadalafil at last follow-up, 24.1% stopped sildenafil due to improvement in PH, 10.3% were lost to follow-up and 17.2% died. None of these outcomes were statistically significantly different from patients in our cohort without trisomy 21. Similar to the patients without trisomy 21 with IPAH, no patient with IPAH and trisomy 21 stopped sildenafil due to improvement in PH. The mortality was high in patients with trisomy 21 and BPD (42.9%). One of these infants had sildenafil stopped due to airway spasms, which may have been attributable to airway congestion from sildenafil in the presence of significant baseline tracheobronchomalacia. This infant died of sepsis and respiratory failure, a few weeks after sildenafil was stopped. Two other patients died from respiratory failure as a primary cause of death.

Patients with PH associated with BPD made up a large proportion of the cohort, with 135 patients included. There was some overlap between the various groups of pulmonary hypertension, with 23 patients with BPD having associated congenital heart disease, some with more than one lesion (11 patients with significant atrial septal defect, 10 with a patent ductus arteriosus, four with a ventricular septal defect and two with pulmonary vein stenosis). The median age of PH diagnosis was 4 months (1week-6.7 years). There was not a significant amount of time between diagnosis and treatment, with a median age at sildenafil initiation of 4 months (1week-6.9 years). The majority of these patients (90%) started sildenafil as monotherapy, and one-quarter required an additional medication added to sildenafil, with a median time to add-on medication of 4 months (1week-4.5 years). 45% of patients with BPD were able to be weaned off sildenafil due to improvement in PH during the follow-up period, with median time on sildenafil of 1.75 years (2weeks to 5.7years). There was the highest overall mortality in this cohort, with 26% (n=35) of patients dying during the follow-up period and 9 of the 35 deaths had death attributed to pulmonary hypertension and the rest from sepsis or worsening lung disease and respiratory failure.

There were 24 patients with PH associated with CDH. The median age at PH diagnosis was significantly younger than the remainder of the cohort at 1 month (1week-9 months) with a

median age at sildenafil initiation of 1.5 months (1week-9months). The majority of patients (91.7%) started sildenafil as monotherapy, and a large proportion (54.2%) required an additional medication, with a median time to add-on medication of 7 months (1 month-4.5 years). Half of the CDH patients (50%) were able to wean off sildenafil after PH improved, with median time to sildenafil discontinuation of 2.1years (4months-4.75years). 29% continued on a PDE 5 inhibitor at last follow-up. Patients with CDH and PH also had a high mortality, with five deaths (21%), two of which were due to pulmonary hypertension and the remaining due to other systemic causes.

Discussion:

Improvement or even resolution of PH during sildenafil therapy has been reported in patients with BPD and CDH.²⁵⁻²⁸ This was true in our study as well, with about half of patients weaned off of sildenafil due to improvement in PH at the end of the study period. The median time to sildenafil discontinuation in this group was 1.75yrs. Although mortality was highest in patients with BPD and CDH in our study, those patients that survive have a high likelihood of weaning off PH medications due to improvement in pulmonary hypertension associated with lung growth and maturation.

IPAH tends to be progressive, and all patients who were started on PDE-5 inhibitors, remained on this medication throughout the study period. Patients with IPAH were the least likely to start sildenafil as first-line targeted PH therapy, as many of these patients were started on more aggressive first line therapy with continuous prostanoid infusions. There were five patients that were initially on a continuous prostanoid infusion that were able to be weaned off once sildenafil was added, some of which were previously described by Melnick et al.¹⁷

The REVEAL registry including children with IPAH demonstrated a 1,3,5 year estimated survival rates from diagnostic catheterization of $96 \pm 4\%$, $84 \pm 5\%$, and $74 \pm 6\%$, respectively with no significant difference in 5-year survival between IPAH and PAH associated with congenital heart disease (5 year survival of $71 \pm 13\%$).^{3,29} In our cohort the 1,3, and 5 year survival in patients with IPAH and PAH associated with congenital heart disease was 98%, 94%, and 90% respectively after sildenafil initiation, which is overall higher than previously reported.

PH associated with CHD was most common in patients with left to right shunts such as atrioventricular canal (AVC), ventricular septal defect (VSD) and patent ductus arteriosus (PDA). Most patients with AV canal defect who were started on sildenafil were repaired, showing the propensity for postoperative pulmonary hypertension in this cohort, and the patients with VSDs and PDAs were mostly unrepaired.

Our study also assessed type of pulmonary hypertension and outcome in patients with trisomy 21. Beghetti et al in a post hoc analysis of trisomy 21 patients in the STARTS-1 trial showed no effect of sildenafil treatment on PVRi or mPAP.³⁰ Although our study did not directly assess the efficacy of sildenafil, comparing outcomes in our study between trisomy 21 and nontrisomy 21 patients showed no statistically significant difference in outcome at

last follow-up. In addition, six patients with trisomy 21 and CHD were unrepaired when started on sildenafil, and four of these patients had improvement in pulmonary hypertension on sildenafil treatment that allowed them to subsequently undergo successful cardiac repair after reduction in pulmonary vascular resistance index to < 6 Wood units $\cdot$ m² and ratio of pulmonary to systemic resistance less than 0.33.

There are many targeted PH-medications approved for adults, and many of these are used off-label in children. Bosentan is currently the only FDA approved targeted PH medication in children, approved in children age three or older with IPAH. Despite the controversy surrounding the use of sildenafil in children, many institutions have continued to use sildenafil as first-line therapy in the majority of patients with pulmonary hypertension, however a large proportion (39%) require additional PH-specific medications.

Out of the 269 patients included in this study, only two patients needed to discontinue sildenafil due to side effects, namely desaturations associated with airway spasm. Both of these patients had PH associated with BPD with one having trisomy 21. This airway spasm was described as episodic desaturation associated with decreased air entry on physical examination, unresponsive to bronchodilators, and required aggressive bagging for resolution of symptoms. It is hypothesized that sildenafil may cause edema in the already compromised airways causing episodic airway occlusion. Although this was a rare side effect of sildenafil, it should be monitored for, especially in patients with PH associated with BPD and in Down syndrome. Priapism, though mentioned by many parents of patients, was never severe enough to need discontinuation of the medication and could be managed by slower up-titration of sildenafil to the ultimate dose. Additionally, facial flushing, headaches, nasal stuffiness and irritability were other symptoms mentioned, without the need to modify therapy.

The STARTS-1 trial showed an increased mortality at three years associated with high dose sildenafil in children with IPAH.¹² Patients at our institution received low dose sildenafil, and overall mortality in our cohort was lower than previously reported data.

The main limitation of this study is the retrospective design. Measurement of efficacy of sildenafil was not deemed possible due to the heterogeneity of the cohort, including many confounding factors including addition of other medications during the study period and variable timing of echocardiograms and cardiac catheterizations in relationship to sildenafil initiation. Side effects that did not lead to sildenafil discontinuation were inconsistently documented, therefore their true frequency could not be accurately determined.

This study shows that sildenafil was well tolerated. Treatment approaches and outcome differ based on type of PH, however with sildenafil remaining as first line treatment for WHO functional class I and II pediatric patients with pulmonary hypertension. Mortality in our cohort was overall lower than previously published mortality associated with various types of PH.^{3,21-25,29} Importantly, patients with Group 3 PH have especially high mortality, but patients that survive have a high likelihood of PH improving over time.

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Abbreviations:

PH	pulmonary hypertension
PDE	phosphodiesterase
PAH	Pulmonary arterial hypertension
FDA	Food and drug administration
IPAH	Idiopathic pulmonary arterial hypertension
CHD	congenital heart disease
EMA	European Medicines Agency
BPD	bronchopulmonary dysplasia
CDH	congenital diaphragmatic hernia
WHO	world health organization
AV	atrioventricular
VSD	ventricular septal defect
PDA	patent ductus arteriosus

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Figure 1:

Kaplan-Meier curve demonstrates overall survival, and compares the survival of WHO Group 1 PH (IPAH, CHD and CTD) and Group 3 PH (BPD and CDH). Survival was worse in Group 3 PH vs. Group 1 PH ($p=0.02$).

Table 1:

Patient characteristics of overall cohort and by type of pulmonary hypertension (PH)

	All patients (n=269)	Patients with IPAH (n=47)	Patients with PAH-CHD (n=53)	Patients with BPD (n=135)	Patients with CDH (n=24)
Male/Female	134/135	16/31	25/28	76/59	10/14
Age at PH diagnosis	6mo (1wk-16.3yrs)	3.9yrs * (1mo-16.3yrs)	10mo (1mo-15.8yrs)	4mo * (1wk-6.7yrs)	1mo * (1wk-9mo)
Age at sildenafil initiation	7mo (1 wk-17.1yrs)	7.6yrs * (2mo-17.1yrs)	1.2yrs (3 wks-16.8yrs)	4mo * (1wk-6.9yrs)	1.5mo * (1wk-9mo)
Follow-up time	3.1yrs (2wks-12.4yrs)	5.7yrs * (2mo-12.4yrs)	3.9yrs (1mo-11.9yrs)	1.9yrs * (2wks-11.5yrs)	3.7yrs (6mo-10yrs)

Amount of time displayed as median (range)

* indicates statistically different from remainder of cohort based on Mann-Whitney test (p<0.05)

IPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD); BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia.

Table 2:

Sildenafil initiation and add-on medications.

		All patients (n=269)	Patients with IPAH (n=47)	Patients with PAH-CHD (n=53)	Patients with BPD (n=135)	Patients with CDH (n=24)
Sildenafil initiation	Monotherapy	228 (84.8%)	26 (55.3%) *	49 (92.5%)	121 (90%)	22 (91.7%)
	Started concurrently with other PH-specific medication	3 (1.1%)	1 (2.1%)	0 (0%)	2 (1.5%)	0 (0%)
	Add-on therapy	38 (14.1%)	20 (42.6%) *	4 (7.5%)	12 (8.5%)	2 (8.3%)
Additional medication added to sildenafil		105 (39.0%)	39 (83.0%) *	19 (35.8%)	33 (24.4%)	13 (54.2%)
Time from sildenafil initiation to add-on medication		6mo (1wk-10.5yrs)	7mo (2wks-8.8yrs)	1.1yrs * (2wks-10.5wks)	4mo (1wk-4.5yrs)	7mo (2mo-4.5yrs)

* indicates significant difference compared to remainder of cohort using chi-squared or Mann-Whitney test (p<0.05)

PH, pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia.

Table 3:

Outcome at last follow-up based on type of pulmonary hypertension (PH)

Type of PH	Total # of patients	On sildenafil or tadalafil	Off sildenafil (PH improved)	Died (all-cause)	Died secondary to PH	Lost to follow-up
IPAH	47	36 (77%)*	0 (0%)*	6 (13%)	4 (9%)	4 (9%)
PAH-CHD	53	26 (49%)	19 (36%)	5 (9%)	3 (6%)	3 (6%)
PAH-CTD	3	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PH-BPD	135	24 (18%)*	61 (45%)*	35 (26%)*	9 (7%)	13 (10%)
PH-CDH	24	7 (29%)	12 (50%)	5 (21%)	2 (8%)	0 (0%)
Other	7	3 (43%)	1 (14%)	3 (43%)	0 (0%)	0 (0%)
Overall	269	99(37%)	93 (35%)	54 (20%)	18 (7%)	20 (7%)

* indicates significant difference compared to remainder of cohort using chi-squared ($p < 0.01$)

PH, pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia.

Table 4:

Type of congenital heart disease and timing of cardiac repair relative to sildenafil initiation.

Type of CHD	Number of patients	Patients repaired prior to sildenafil initiation	Patients repaired after sildenafil initiation	Patients unrepaired at last follow-up
Atrioventricular canal	22	15	5	2
Ventricular septal defect (VSD)	7	2	2	3
Patent ductus arteriosus	6	1	2	3
TOF/PA/MAPCAs	5	5	0	0
Truncus arteriosus	3	3	0	0
Aortic coarctation	3	3	0	0
D-TGA	2	2	0	0
Mitral stenosis	2	2	0	0
AP window	1	0	0	1
IAA/VSD	1	1	0	0
Pulmonary vein stenosis	1	1	0	0

TOF/PA/MAPCAs, Tetralogy of Fallot with pulmonary atresia and major aortopulmonary collaterals; D-TGA, D-transposition of the great arteries; AP, aortopulmonary; IAA, interrupted aortic arch.

Table 5:

Type of pulmonary hypertension (PH) and outcome in patients with trisomy 21.

Type of PH	Total # of patients	Outcome at last follow-up			
		On sildenafil or tadalafil	Stopped sildenafil due to PH improvement	Lost to follow-up	Died
IPAH	4 (13.8%)	2 (50%)	0 (0%)	1 (25%)	1 (25%)
PH-BPD	7 (24.1%)	2 (28.6%)	2 (28.6%)	0 (0%)	3 (42.9%)
PAH-CHD	18 (62.1%)	10 (55.5%)	5 (27.8%)	2 (11.1%)	1 (5.5%)
Overall	29	14 (48.3%)	7 (24.1%)	3 (10.3%)	5 (17.2%)