A Retrospective Review of Infants Receiving Sildenafil

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OBJECTIVE The purpose of the study was to assess mortality in an infant population receiving sildenafil.

METHODS A retrospective review of hospitalized infants at Children's Hospital Los Angeles who received sildenafil between 2008 and 2012 was conducted. Patient characteristics, comorbidities, and treatment characteristics were analyzed. Primary outcome was mortality at discharge. Sildenafil dosage ranges were based on the Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension trial and were categorized as small (<1.5 mg/kg/day), medium (1.5–3.75 mg/kg/day), large (3.76–7.5 mg/kg/day), and very large (>7.5 mg/kg/day).

RESULTS A total of 147 infants were studied. A total of 82% of patients had severe pulmonary hypertension. Our data revealed 29% mortality at discharge. Mortality increased with increasing sildenafil dosage: 14% (small), 19% (medium), 49% (large), and 90% (very large). On multivariate analysis of sildenafil dosage, other pulmonary hypertension therapies, presence of persistent cardiac shunts, and duration of sildenafil, odds of dying were significantly higher with combined high and very high sildenafil dosage groups compared with combined low and medium dosage groups (OR, 13.2; CI, 4.4–39.5; $p < 0.0001$).

CONCLUSION Sildenafil was given to critically ill infants with multiple risk factors for mortality. Although higher doses cannot be causally related to mortality, there appears to be no added benefit by escalating the sildenafil dose.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; CHLA, Children's Hospital Los Angeles; FDA, US Food and Drug Administration; ICU, intensive care unit; IVS, inter-ventricular septum; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; RV, right ventricle; RVP, right ventricular pressure; STARTS-1, Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension Trial; STARTS-2, Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension Trial–2

KEYWORDS infants; mortality; pediatric pulmonary hypertension; sildenafil

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Introduction

Pulmonary hypertension (PH) is a cause of significant morbidity and mortality.^{1–4} Studies on the management of PH are largely from the adult literature, with few pediatric randomized or prospective trials^{5,6}; however, pediatric PH is increasingly being recognized for its unique pathophysiology and phenotype. There have been recent attempts to make a separate classification system of pediatric PH.^{4,7} Sildenafil, a phosphodiesterase-5 inhibitor, has been widely used as an off-label medication for the treatment of pediatric PH but lacks US Food and Drug Administration (FDA) approval in the pediatric population. Moreover, the recently published data from the Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension Trials (STARTS-1 and STARTS-2) have raised controversy about the safety and efficacy of sildenafil in the pediatric population, resulting in an FDA black box warning for the use of sildenafil in the 1- to 17-year age group,^{8–11} raising concerns among physicians caring for pediatric

patients with pulmonary arterial hypertension.¹²

Pulmonary hypertension in the infant population commonly presents as persistent PH of the newborn (PPHN) or secondary to cardiac disease, developmental anomalies with pulmonary hypoplasia, or chronic lung disease of infancy. The neonatal population represents a unique subgroup in pediatrics where the physiologic transition of fetus to newborn interplays with perinatal risk factors, along with parameters of lung growth and development.⁴ Small, randomized trials have assessed the off-label use of sildenafil for PPHN in the neonatal and infant population, but this population was excluded from the STARTS trials.^{5,13,14} In clinical practice it was observed that infants treated within the Children's Hospital Los Angeles's (CHLA's) intensive care unit (ICU) with sildenafil survived and were seen in the outpatient pediatric pulmonology clinic. We conducted a retrospective review of infants receiving sildenafil in order to compare our outpatient clinical experience with mortality rates during a 5-year period in our hospital's intensive care unit.

Materials and Methods

We conducted a retrospective review of hospitalized infants younger than 1 year at CHLA who received sildenafil during the period of January 1, 2008, to December 31, 2012. CHLA is a large tertiary care center with a level III neonatal intensive care unit serving a large referral basin within the greater Los Angeles area. Patients were identified from inpatient pharmacy records as having received at least 1 dose of sildenafil. Patients with complex congenital heart disease were excluded. The study was approved by the CHLA Institutional Review Board (13-00071).

Data Collection. Medical records were reviewed for patient demographic information, including sex, race, and ethnicity, gestational age, birth weight, age at admission, age at start of sildenafil, age at diagnosis of PH, and duration of hospitalization. Birth weight was categorized as <2.5 kg and ≥2.5 kg. Gestational age was defined as preterm if <37 weeks and full term if ≥37 weeks.

Medical records were reviewed for the following comorbid conditions assigned and documented by the treating neonatologist: PH, chronic lung disease, bronchopulmonary dysplasia (BPD), idiopathic pulmonary arterial hypertension, meconium aspiration, congenital diaphragmatic hernia, pulmonary hypoplasia, alveolar capillary dysplasia, simple congenital heart disease, chromosomal/genetic abnormality, and necrotizing enterocolitis. Severity of PH was graded as mild, moderate, or severe as documented by the referring hospital or at the time of admission after reviewing echocardiograms for tricuspid regurgitation jet, right ventricular pressure (RVP), pulmonary artery pressure, cardiac shunts, shape of interventricular septum (IVS), dilation of right ventricle (RV), and cardiac catheterization data. Pulmonary hypertension was graded as mild to moderate if IVS was rounded or mildly flattened and/or there was mild to moderate dilation of RV and/or tricuspid regurgitation jet was less than 3 m/sec, RVP less than 40 mm Hg; severe if there was systemic or suprasystemic RVP and/or tricuspid regurgitation jet was greater than 3 m/sec and/or IVS was flattened or deviated to left ventricle and/or there was the presence of bidirectional shunt. If PH severity was not documented in the echocardiogram or cardiac catheterization reports, the echocardiogram information was reviewed by 2 pediatric cardiologists to determine PH severity. Chronic lung disease was defined based on provider-assigned diagnosis of chronic lung disease in the patient's medical records. Bronchopulmonary dysplasia was graded as mild, moderate, or severe according to the National Institutes of Health consensus definition: mild BPD with no oxygen requirement; moderate, as an oxygen requirement greater than 21% F_{iO_2} ; and severe, as an oxygen requirement greater than 21% F_{iO_2} via positive pressure ventilation at corrected 36 weeks

or 56 days postnatal age.¹⁵ Simple congenital heart disease included atrial septal defect, ventricular septal defect, and/or patent ductus arteriosus. If the simple congenital heart disease did not resolve spontaneously, or after medical or surgical intervention, patients were defined as having persistent cardiac shunts. Complex heart disease patients were not included in our study because they represent a different pathophysiology and complexity of disease.

Treatment characteristics included respiratory support during hospitalization and at the time of discharge, extracorporeal membrane oxygenation, use of vaso-pressors, diuretics, and use of the other medications epoprostenol (prostacyclin) and bosentan (endothelin 1 receptor antagonist). Data were collected for dosage and duration of sildenafil. If sildenafil was started at an initial dosage and titrated during the hospitalization, the final dosage of sildenafil was used for analysis. Sildenafil dosages were based on the STARTS-1 trial and were classified as small (<1.5 mg/kg/day), medium (1.5–3.75 mg/kg/day), and large (3.76–7.5 mg/kg/day). These dosage groups are expected to achieve target concentrations of 47, 140, and 373 mcg/L, with approximately 53%, 77%, and 90% inhibition of phosphodiesterase-5 inhibitor activity, respectively.^{8,16,17} In addition, a fourth category of very large (>7.5 mg/kg/day) was used for dosages larger than the dosage ranges used in the STARTS-1 trial but recommended in the Lexi-Comp online formulary, Children's Hospital Los Angeles.¹⁸ For patients who received intravenous sildenafil, the oral dose equivalent (10 mg of intravenous sildenafil equal to 20 mg oral dose) was used for analysis.¹⁸ Patients treated with oral sildenafil were given a 2.5 mg/mL suspension extemporaneously prepared by the hospital pharmacy.

The primary end point of our study was mortality at discharge. General mortality statistics for the CHLA ICUs for the same study period, 2008–2012, were determined.

Statistical Analysis. Univariate analysis was conducted to compare the status at discharge, deceased versus alive. Logistic regression was used for all continuous and categorical variables. All quantitative data were expressed as median with IQR. Continuous variables were assessed for linearity, and duration of sildenafil was transformed to natural log scale. Small and medium dosage groups were combined based on the results from the STARTS trials, in which they had improved survival compared with the large dosage group.^{8,9} Because of the small sample size in the very large sildenafil dosage group, large and very large dosage groups were combined. The interaction and confounding for each variable was assessed one at a time in the logistic regression model. Further, multivariate logistic regression was performed to adjust for all potential confounders. A *p* value of ≤0.05 was considered to be statistically significant. All tests were 2-sided. The statistical software

Table 1. Patient Characteristics

	Alive (n = 104)	Deceased (n = 43)
Sex, n (%)		
Male	58 (56)	25 (58)
Female	46 (44)	18 (42)
Ethnicity, n (%)		
Hispanic	56 (54)	18 (42)
Non-Hispanic white	14 (13)	8 (19)
Asian/Pacific	8 (8)	4 (9)
Black	12 (12)	7 (16)
Other	14 (13)	6 (14)
Gestational age, n (%)		
Preterm	48 (46)	18 (41)
Full-term	56 (54)	25 (59)
Birth weight, n (%) [*]		
<2.5 kg	31 (38)	17 (49)
≥2.5 kg	51 (62)	18 (51)
Age at admission, days, median (IQR)	2 (1–97)	4 (1–101)
Duration of hospitalization, days, median (IQR)	42 (18–109)	21 (5–37)
Age at discharge, days, median (IQR)	94 (30–187)	36 (16–159)
Age at start of sildenafil, days, median (IQR)	11 (2–116)	17 (3–125)
Duration of sildenafil, days, median (IQR)	20 (11–61)	11 (4–31)

^{*} Percentage calculated using available data: alive, n = 82; deceased, n = 35.

STATA/IC 13 (StataCorp, College Station, TX) was used for data analysis. Chi-square goodness-of-fit for overall fit as well as regression diagnostics for individuals were performed. Sensitivity analysis was assessed for the main effects model. Kaplan-Meier survival analysis was estimated for sildenafil dosage categories against duration of sildenafil use in days.

Results

During the study period, 526 patients received sildenafil during hospitalization at CHLA. There were 392 infants, of whom 147 did not have complex congenital heart disease and met inclusion criteria for the study. Our data revealed 29% mortality at discharge. Table 1 describes the demographic characteristics of the 2 groups, alive and deceased. Additional comorbidities for the 2 groups are listed in Table 2. The groups were similar in sex, ethnicity, gestational age, and birth weight. Treatment characteristics and respiratory support for the 2 groups are described in Table 3. Patients who died were almost all on vasopressors (98%), and 37% were also on other medications for PH.

On univariate analysis of risk factors for mortality (Table 2), use of other PH therapies (OR, 4.1; CI, 1.7–10;

p = 0.002) resulted in significantly higher odds of dying. Odds of dying were significantly higher in combined large and very large dosage groups compared with small and medium dosage groups (OR, 6.8; CI, 3.1–15; p < 0.0001). Patients with persistent cardiac shunts had higher risk of mortality compared with patients whose shunts closed during the hospitalization (OR, 3.2; CI, 1.4–7.4; p = 0.007). Presence of chronic lung disease (OR, 0.4; CI, 0.2–0.8; p = 0.006) and meconium aspiration at birth (OR, 0.3; CI, 0.1–0.9; p = 0.049) were associated with a lower risk of mortality.

On multivariate analysis, odds of dying were statistically significantly higher with sildenafil combined large and very large dosage groups after adjusting for other variables (OR, 13.2; CI, 4.4–39.5; p < 0.0001). Use of other PH therapies had a significantly higher risk of mortality (OR, 5.1; CI, 1.4–18.4; p = 0.012). Patients with persistent cardiac shunts had higher odds of dying compared with patients with closed cardiac shunts (OR, 2.6; CI, 0.9–7.8; p = 0.08). One outlier was noted on regression diagnostics and was excluded in the multivariate model. There was no evidence of lack of fit in the model from χ^2 goodness-of-fit test (p = 0.92). Based on receiver-operating characteristics curve analysis, our model provided an excellent discrimination between

Table 2. Comorbidities

	Alive (n = 104)	Deceased (n = 43)	Unadjusted OR (95% CI)
Severity of pulmonary hypertension*			
Mild to moderate , n (%)	20 (20)	5 (12)	1.0 (reference)
Severe, n (%)	76 (78)	36 (88)	1.89 (0.66–5.45)
IPAH, n (%)	6 (6)	2 (5)	0.79 (0.15–4.11)
Chronic lung disease, n (%)	67 (64)	17 (40)	0.36 (0.17–0.75)¶
Severe bronchopulmonary dysplasia†, n (%)	31 (30)	9 (21)	1.59 (0.29–8.56)
Meconium aspiration, n (%)	25 (24)	4 (9)	0.32 (0.10–0.99)¶
Congenital diaphragmatic hernia, n (%)	20 (19)	12 (28)	1.63 (0.71–3.71)
Unrepaired CDH‡, n (%)	0 (0)	6 (50)	—
Pulmonary hypoplasia, n (%)	39 (38)	16 (37)	0.99 (0.47–2.06)
Alveolar capillary dysplasia, n (%)	1 (1)	4 (9)	10.56 (1.14–97.47)¶
Simple congenital heart disease, n (%)	94 (90)	35 (81)	0.47 (0.16–1.27)
Persistent cardiac shunt§, n (%)	40 (43)	24 (71)	3.18 (1.37–7.4)¶
Chromosomal/genetic abnormality, n (%)	18 (17)	10 (23)	1.5 (0.62–3.61)
Necrotizing enterocolitis, n (%)	2 (2)	1 (2)	1.21 (0.11–13.75)

CDH, congenital diaphragmatic hernia; IPAH, idiopathic pulmonary arterial hypertension

* Percentage calculated using available data: alive, n = 96; deceased, n = 41.

† Percentage calculated using available data: alive, n = 103; deceased, n = 43.

‡ Percentage calculated using available data: alive, n = 93; deceased, n = 34.

§ Percentage calculated using the number of patients with comorbid condition.

¶ p value ≤ 0.05.

the 2 outcome groups (area under the curve = 0.88).

Kaplan-Meier survival (Figure) for sildenafil dosages showed that there was a statistically significant difference in survival among different dosages of sildenafil ($p = 0.0002$). The mortality rates associated with sildenafil dosage groups were 14% (small), 19% (medium), 49% (large), and 90% (very large). When compared to the mortality statistics of CHLA's ICUs for the same period, the mortality in our population was 4.6 compared with 1.3 per 1000 patient days for the ICUs. During the 5-year study period, the number of patients started on sildenafil increased from 16 patients in 2008 to 43 patients in 2012. The overall ICU mortality for this period remained stable, with a range 1.76 to 2.04 per 1000 patient days.

Discussion

Our retrospective study assessed the mortality of patients younger than 1 year who received sildenafil in a major tertiary children's hospital. We hypothesized that there would be low mortality in the infant population that received sildenafil from 2008 to 2012; however, our study revealed a higher-than-expected mortality rate of 29%. We evaluated clinical factors to determine what predicts mortality, but none were significantly different within the alive versus deceased groups. We found that infants who received sildenafil were medi-

cally complex, with a significant number of patients with severe PH, prematurity, BPD requiring vasopressors, and mechanical ventilation. Patients who died with underlying conditions, such as alveolar capillary dysplasia, unrepaired severe congenital diaphragmatic hernia, or chromosomal and genetic abnormalities, inherently had poor prognoses. The major limitation of our study is that we do not have a matched control population to determine whether patients with the same disease severity not receiving sildenafil had improved survival. Another limitation of the study was variability in the classification of PH severity at outside referring institutions due to a variation in protocols and interpretation. The echocardiograms from outside institutions were not available for review.

There was a 13.2-fold increased risk of mortality for the combined large and very large dosage groups on multivariate analysis. Group mortality rates increased as sildenafil dosing increased from small (14%) to medium (19%) to large (49%) to very large (90%) in this infant population, consistent with the trend in the STARTS-2 trial, with low, medium, and high dosage mortality being 9%, 14%, and 22%, respectively.⁸ However, our all-group mortality rate of 29% is higher than the 20% mortality reported by Mourani et al¹⁹ in their retrospective review of PH in infants with chronic lung disease. The larger population size in our study and the fact that some of

Table 3. Treatment Characteristics

	Alive (n = 104)	Deceased (n = 43)
Sildenafil dosage groups, n (%)		
Small (<1.5 mg/kg/day) and medium (1.5–3.75 mg/kg/day)	85 (82)	17 (40)
Large (3.76–7.5 mg/kg/day) and very large (>7.5 mg/kg/day)	19 (18)	26 (60)
Mechanical ventilation, n (%)	101 (97)	43 (100)
ECMO, n (%)	35 (34)	16 (37)
Respiratory support at discharge, n (%)		
Nasal cannula	44 (42)	1 (2)
Mechanical ventilation	27 (26)	41 (95)
Non-invasive ventilation	4 (4)	0 (0)
Use of vasopressors, n (%)	89 (86)	41 (98)
Use of another PH medication*, n (%)	11 (11)	16 (37)

ECMO, extracorporeal membrane oxygenation; PH, pulmonary hypertension

* Epoprostenol and bosentan.

our patients were referred with a prior diagnosis of PH (34%), who may not have been on PH therapy prior to transfer, may be the reasons for the higher mortality. Further, patients who died had a shorter duration of sildenafil use, which may reflect a more critically ill population of infants. It is also possible that patients with more severe disease received the larger sildenafil dosages in an effort to obtain a clinical response but were unlikely to benefit from dosage escalation.

The presence of a persistent cardiac shunt was associated with significantly increased odds of mortality (OR, 3.2) on univariate analysis but in the final multivariate

model, the odds of mortality were not statistically significant. Because duration of sildenafil use was also part of the multivariate model it is possible that cardiac shunts had closed over time and were no longer significant.

The results of the STARTS-1 and STARTS-2 trials have stirred debate in the PH community about the safety of sildenafil use in the pediatric population. However, the STARTS trials did not study infants younger than 1 year, leaving questions as to the utility of sildenafil in this population. Because of the constraints of performing clinical drug trials in neonates and infants, the unique pathophysiology of PH in this population, along with few

Figure. Kaplan-Meier survival estimation by sildenafil doses.

Sildenafil dose categories: - - - small (<1.5 mg/kg/day); ----- medium (1.5–3.75 mg/kg/day); - - - - large (3.76–7.5 mg/kg/day); and ... very large (>7.5 mg/kg/day).

other medication options for treatment, we attempted to fill a knowledge gap as to whether there were any associated clinical risk factors between mortality and sildenafil use in infants. This study included infants at a quaternary hospital who are medically complex, with severe disease, who would be more likely to receive higher doses of sildenafil and would be at a higher risk of death irrespective of sildenafil dose. However, no specific factor in this patient population predicted an increased risk of mortality except for sildenafil dose, suggesting the need for dosing guideline criteria in infants.

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