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Sildenafil and Retinopathy of Prematurity Risk in Very Low Birth Weight Infants

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Abstract

Objective—To examine the effect of sildenafil therapy on development of severe retinopathy of prematurity (ROP) requiring surgical intervention in premature infants.

Study Design—We identified premature infants who were discharged from Pediatrix Medical Group neonatal intensive care units from 2003–2012 and who received an ophthalmologic exam. We matched each infant exposed to sildenafil prior to first eye exam to three non-exposed infants using propensity scoring to control for differences in baseline infant characteristics. We evaluated the association between sildenafil exposure and development of severe ROP using conditional logistic regression.

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Result—Of the 57815 infants meeting inclusion criteria, 88 were exposed to sildenafil. We matched 81/88 (92%) sildenafil-exposed with 243 non-exposed infants. There was no difference in the proportion of infants who developed severe ROP in the sildenafil-exposed vs. non-exposed groups (17/81 [21%] vs. 38/243 [16%], P=0.27). On adjusted analysis, there was no difference in severe ROP in the sildenafil-exposed versus non-exposed infants (odds ratio=1.46, 95% confidence interval=0.76–2.82, P=0.26).

Conclusion—We did not observe an association between risk of severe ROP and sildenafil exposure prior to first eye exam in this cohort of premature infants.

INTRODUCTION

Sildenafil is increasingly used off-label for treatment of pulmonary hypertension (PH) of various etiologies in infants and children.[1] Persistent pulmonary hypertension of the newborn (PPHN) and PH associated with congenital heart disease, chronic lung disease, or congenital diaphragmatic hernia are common conditions treated with sildenafil therapy in term and preterm infants.[2]

The therapeutic effect of sildenafil in PH occurs through its inhibitory action on phosphodiesterase type 5 (PDE5), which results in nitric oxide (NO)-mediated vasorelaxation.[3] Despite the high selectivity of sildenafil for PDE5 enzymes, it also inhibits the retina-specific phosphodiesterase type 6 (PDE6) with one-tenth the potency compared with PDE5.[3] Expression of PDE6 enzymes in rod and cone photoreceptors of retinal tissue, as well as the discovery of PDE5 enzymes on retinal and choroid vasculature, have raised concerns about potential adverse effects of sildenafil on the developing eye of premature infants.[3-5]

Because of the increasing use of sildenafil despite the lack of population-specific safety data,[6] we sought to examine the association between sildenafil therapy and the development of severe retinopathy of prematurity (ROP), requiring therapy in hospitalized, very low birth weight (VLBW) infants (1500 g).

METHODS

Data Source

Data were obtained from the Pediatrix Medical Group Data Warehouse, which prospectively captures information from an electronic medical record of daily progress notes and other documentation of clinicians involved in the care of infants (https://www.pediatrix.com/PediatrixUniversity). We included all inborn infants 32 weeks gestational age (GA) and 1500 g birth weight (BW) who received an ophthalmologic exam and were discharged from one of the 326 North American neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group from 2003–2012. Infants who started sildenafil therapy after their initial ROP examination or after 36 weeks postmenstrual age were excluded. Information regarding maternal history, infant demographics, respiratory and hemodynamic support, medications, culture results, and ophthalmologic exams were obtained.

Definitions

The primary outcome of our study was severe ROP, defined as any ROP requiring surgical intervention, cryotherapy, laser therapy, or treatment with bevacizumab. We defined sildenafil exposure as any sildenafil therapy prior to the initial ophthalmologic examination, and calculated cumulative exposure to sildenafil as the number of days of exposure to sildenafil prior to the initial ophthalmologic examination. We defined history of bacteremia as a binary variable: if the infant had at least one positive blood culture with organisms not considered a contaminant prior to or on the infant day of hospitalization. We defined cumulative daily inotropic support, mechanical ventilation, and supplemental oxygen as the cumulative days of exposure to any inotropic drug (dobutamine, dopamine, epinephrine, milrinone/amrinone, norepinephrine), any mechanical ventilation, and any fraction of inspired oxygen (FiO2) >21% up until each infant day of hospitalization. We defined small for gestational age (SGA) as previously described.[7]

Statistical Analysis

We used medians with interquartile ranges and counts with percentages to describe continuous and categorical variables, respectively. We compared the distribution between infants with and without sildenafil exposure using Wilcoxon rank sum, chi-square, and Fisher's exact tests where appropriate. Because more severely ill infants are more likely to receive sildenafil therapy and are at higher risk of developing ROP, we used propensity scores to match infants in a 3:1 ratio (non-exposed:exposed) to ensure comparison of similar infants.[8] A propensity score for sildenafil exposure or non-exposure on each infant day of hospitalization was estimated using multivariable logistic regression including covariates that might predict both sildenafil therapy and ROP risk: GA in weeks, postnatal age (PNA) in days, sex, race/ethnicity, Apgar score at 5 minutes, SGA status, antenatal steroid exposure, bacteremia, mechanical ventilation, inotropic support, and supplemental oxygen, as defined above.[9] We matched infants on the first day of sildenafil exposure with three non-exposed infants using nearest-neighbor matching without replacement. Matching was allowed only if the difference in propensity score between case and control was <0.01. We assessed covariate balance across treatment groups by comparing covariate means, histograms, and Kernel density plots of propensity scores across the two groups. We used Stata's psmatch2 routine that implements full Malhanobis and a variety of propensity score matching methods.[10] We compared the distribution of covariates between the two groups after propensity matching using Wilcoxon rank sum, chi-square, or Fisher's exact tests where appropriate. We used conditional (fixed effects) logistic regression to evaluate the association between any sildenafil exposure prior to ROP evaluation and risk of severe ROP conditioned on the matched pair. In an a priori defined secondary analysis, we used conditional logistic regression to evaluate the association between risk of severe ROP and cumulative duration of sildenafil exposure as defined above, and categorized as 0 days, 1–7 days, 8–14 days, and >14 days. The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the datasets used did not contain any patient identifiers.

RESULTS

We identified 57815 VLBW infants meeting inclusion criteria, of whom 88 (0.2%) were exposed to sildenafil (Figure 1). The median (25th, 75th percentile) BW and GA of the entire cohort were 1006 g (830, 1270) and 28 weeks (26, 30), respectively. Median GA and BW were lower in infants exposed to sildenafil compared with those not exposed (GA 25 weeks [24, 27] vs. 28 weeks [26, 30], *P*<0.001 and BW 665 g [535, 813] vs. 1006 g [833, 1270], *P*<0.001). Infants exposed to sildenafil were also more likely to be SGA, had lower 5-minute Apgar scores, and more exposure to inotropic drugs, ventilator support, and supplemental oxygen compared with those not exposed to sildenafil (Table 1). The proportion of infants who developed severe ROP was higher in the sildenafil-exposed compared with the non-exposed group—18/88 (21%) vs. 2546/57727 (4%), *P*<0.001.

We successfully matched 81/88 (92%) sildenafil-exposed with 243/57 727 (<1%) non-exposed infants. Following matching, characteristics between groups were well balanced, and there were no statistically significant differences between the sildenafil-exposed and non-exposed infants in baseline demographics, cumulative days of inotropic exposure, mechanical ventilation, or oxygen therapy. Median PNA at the time of severe ROP therapy also did not differ significantly between sildenafil-exposed and non-exposed infants (93 days [74, 99] vs. 87 days [73, 102], *P*=0.95), nor did median PMA (37 weeks [36, 38] vs. 37 weeks [35, 39], *P*=0.86).

After matching, the proportion of infants who developed severe ROP was similar in the sildenafil-exposed vs. non-exposed infants (17/81 [21%] vs. 38/243 [16%], *P*=0.27). There was no significant difference in the odds of severe ROP in the sildenafil-exposed versus non-exposed infants (odds ratio=1.46, 95% confidence interval=0.76–2.82, *P*=0.26). The median duration of sildenafil therapy was 10 days (2, 31). Duration of sildenafil therapy was 1–7 days in 35/81 infants (43%), 8–14 days in 10/81 infants (12%), and >14 days in 36/81 infants (44%). Increasing duration of sildenafil exposure prior to initial eye exam was also not associated with increased risk for development of severe ROP compared with the non-exposed infants (Table 2).

DISCUSSION

We present the results of a propensity score-matched, case-control study of hospitalized VLBW infants exposed to sildenafil prior to their first ROP evaluation. Following matching, groups were well balanced for available risk factors of ROP, and we observed no difference in the risk of severe ROP in infants exposed to sildenafil. This observation remained when using duration of sildenafil exposure as a predictor of severe ROP.

Reported potential ocular adverse effects of sildenafil in infants are limited. A case report described a 26-week premature infant who developed aggressive ROP while receiving sildenafil therapy.[5] The infant had a complicated clinical course, including three episodes of bacterial and fungal sepsis, and required 100% oxygen therapy for up to 32 weeks corrected GA. In a retrospective, single-center, case-control study, 17 infants <30 weeks gestation exposed to sildenafil were compared with 51 control infants for progression of ROP or need

for laser treatment.[11] Sildenafil was started at median of 36 weeks corrected GA and continued for a median duration of 52 days. The treated and untreated groups were not similar in their baseline characteristics, with infants in the sildenafil group requiring more respiratory support. The time of ROP assessment relative to the timing of sildenafil therapy was unclear. This study did not observe any effect of sildenafil on ROP progression or need for laser treatment. Another retrospective, single-center study assessed 22 term and later preterm infants not at risk for ROP or for development of any other ocular complications following 2–36 weeks of treatment with sildenafil.[12] All infants received an ophthalmologic assessment at chronological age of 2–40 weeks indicated specifically due to sildenafil therapy. This study did not find any ocular complications related to the use of sildenafil.

We report the first multicenter study evaluating the association between early sildenafil exposure and severe ROP. In addition to larger sample size, we were able to control for several known ROP risk factors in our analysis through propensity score matching. This matching was essential given the significant differences in ROP risk factors between the unmatched populations. Our results are in agreement with the existing limited evidence that sildenafil therapy does not increase the risk for development of severe ROP in premature infants.

Sildenafil is a predominant PDE5 inhibitor with vasodilatory properties in widespread use since its initial approval in adults.[13] The promising results of sildenafil for treatment of PH in adults have resulted in its increasing use in infants.[1,2] In a recent review of medication use in hospitalized infants, sildenafil had the second highest relative increase in use, up by over 11-fold, from 0.2 to 2.3 per 1000 infants from 2005–2010.[6] Reports of visual disturbances in adults treated for erectile dysfunction, although mostly mild and transient, drew considerable attention to the potential adverse effects of sildenafil on the ocular system.[14_18] These effects have been attributed to its cross-inhibition of the retinal photoreceptor-specific PDE6 enzyme, as well as the recent discovery of PDE5 enzymes in the retinal and choroidal vasculature.[19] Alterations of the NO signaling pathway, increase in intraocular pressure, changes in choroidal blood flow or thickness, and variation of retinal perfusion have been raised as potential mechanisms for the observed adverse effect of sildenafil on the ocular system.[20_22] NO is an important determinant of choroidal and retinal blood flow in the developing eye of premature infants. It is known to have inhibitive effect on retinal vascular obliteration and subsequently proliferative retinopathies, but it can also increase neoangiogenic activity via vascular endothelial growth factor (VEGF)-induced angiogenesis.[23] It is not known whether any of these sildenafil induced changes in NO signaling pathways affects the development and progression of ROP.

Our study is limited in its retrospective nature and data obtained from electronic documentation of clinical care rather than from a prospectively established research database. Most importantly, at the time of this analysis, sildenafil dosing and indication were not completely captured in the database, and we were unable to examine any potential associations between sildenafil dosing, exposure, and ROP risk. This limitation is particularly relevant as the ocular safety of sildenafil may be dose-dependent. Dose dependency has been suggested in rat models of PDE-6 expression, which is increasingly down regulated with higher doses of sildenafil.[24,25] Moreover, details from the ocular

examination, including exact timing of diagnosis or early findings suggestive of increased ROP risk and severity and extent of ROP, were not available, and we were unable to stratify infants according to the International Classification of Retinopathy of Prematurity system.[26] Instead, we had to use ROP intervention during hospitalization as a surrogate for severity, and the decision to treat ROP was at the discretion of the local provider. Outpatient follow up data to identify later diagnoses of ROP or resulting blindness were also not available. We examined infants with early sildenafil exposure and used propensity score matching, resulting in balanced groups with regard to baseline risk of ROP.[27] Our results add to the safety profile of sildenafil as an off-label medication in infants and show that infants who were exposed to sildenafil at a very young age did not have a higher risk for development of severe ROP.

CONCLUSION

We did not observe an increased risk of ROP in premature infants treated with sildenafil prior to their first ROP exam. These results support the conduct of future prospective trials characterizing the safety and efficacy of sildenafil in premature infants.

Acknowledgments

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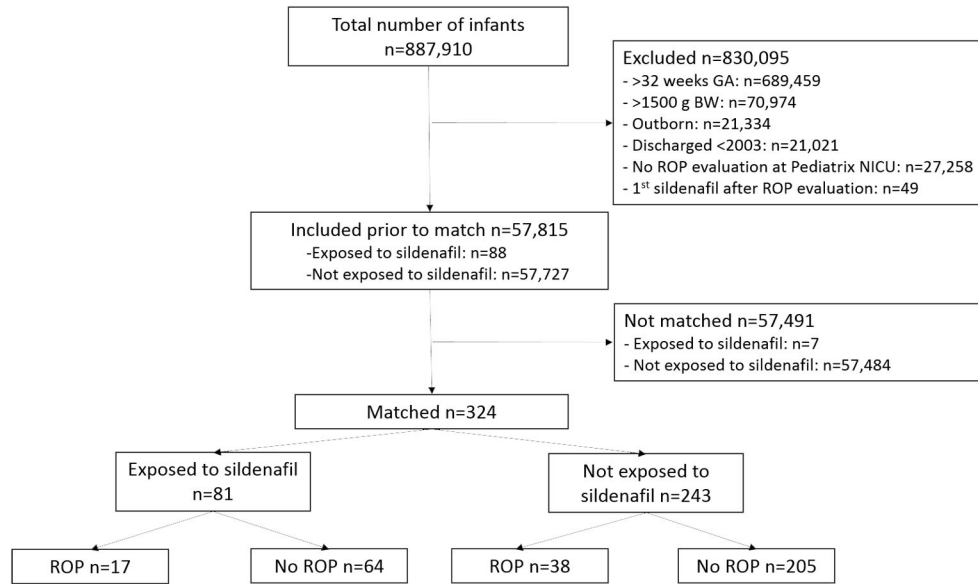
Figure 1.
Study flow diagram. Abbreviations: BW, birth weight; GA, gestational age; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

Table 1

Baseline and clinical characteristics

	All Infants Prior to Match			Matched Infants		
	Sildenafil-exposed (N=88)	Non-exposed (N=57 727)	P^*	Sildenafil-exposed (N=81)	Non-exposed (N=243)	P^*
Gestational age (weeks)			<0.001			0.54
<26	47 (53%)	9338 (16%)		44 (54%)	132 (54%)	
26–28	34 (39%)	22 644 (39%)		30 (37%)	98 (40%)	
29–32	7 (8%)	25 745 (45%)		7 (9%)	13 (5%)	
Male	49 (56%)	29 154 (51%)	0.33	45 (56%)	148 (61%)	0.40
Race/ethnicity			0.30			0.45
White	42 (49%)	27 039 (48%)		40 (49%)	98 (40%)	
Black	29 (34%)	15 476 (28%)		28 (35%)	90 (37%)	
Hispanic	12 (14%)	10 184 (18%)		12 (15%)	49 (20%)	
Other	2 (2%)	3143 (6%)		1 (1%)	6 (3%)	
Apgar score at 5 minutes			<0.001			0.81
0–3	9 (11%)	1804 (3%)		9 (11%)	32 (13%)	
4–6	31 (37%)	8905 (16%)		30 (37%)	82 (34%)	
7–10	44 (52%)	46 076 (81%)		42 (52%)	129 (53%)	
SGA	28 (32%)	10 554 (18%)	<0.001	25 (31%)	82 (34%)	0.63
Antenatal steroid	80 (91%)	48 306 (84%)	0.07	74 (91%)	221 (91%)	0.91
Bacteremia	22 (25%)	7942 (14%)	0.002	20 (25%)	72 (30%)	0.39
Illness severity, (days) †						
Inotrope exposure	3 (0, 8)	0 (0, 0)	<0.001	3 (0, 7)	3 (0, 8)	0.61
Mechanical ventilation	32 (17, 53)	2 (0, 16)	<0.001	33 (19, 52)	32 (8, 53)	0.54
Oxygen exposure	42 (20, 61)	15 (2, 53)	<0.001	40 (20, 60)	34 (13, 62)	0.55
PNA at ROP therapy, (days) †	93 (75, 97)	76 (65, 87)	0.02	93 (74, 99)	78 (73, 102)	0.95

Abbreviations: SGA, small for gestational age; PNA, postnatal age; ROP, retinopathy of prematurity.

*
Calculated from chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

†
Median (25th, 75th percentiles).

Table 2

Frequency and adjusted odds ratio of severe ROP in matched infants

	ROP n (%)	Adjusted Odds Ratio (95% Confidence Interval)
Sildenafil exposure status		
Non-exposed	38/243 (16%)	REFERENCE
Exposed	17/81 (21%)	1.46 (0.76–2.82)
Days of exposure to sildenafil		
0	38/243 (16%)	REFERENCE
7	6/35 (17%)	0.83 (0.30–2.26)
7–14	3/10 (30%)	5.61 (0.55–57.3)
>14	8/36 (22%)	2.04 (0.73–5.69)

Abbreviation: ROP, retinopathy of prematurity.