Sildenafil and Retinopathy of Prematurity in Preterm Infants with Bronchopulmonary Dysplasia

David Aboudi, MPH[1,2], Nithya Swaminathan, MBBS[3,4], Heather Brumberg, MD, MPH[1], Qiuhu Shi, MS, PhD[2], Deborah Friedman, MD[1], Boriana Parvez, MD[1], and Usha Krishnan, MD, DM, FAHA[1,3]

Objective To assess whether sildenafil is associated with worsening retinopathy of prematurity (ROP) in very low birth weight (VLBW) infants (≤1500 g) with bronchopulmonary dysplasia (BPD).

Study design This retrospective case-control study included VLBW infants admitted to the neonatal intensive care unit between January 1, 2006, and December 31, 2012. Each infant treated with sildenafil was assigned 3 unexposed controls matched for gestational age, birth weight, and BPD diagnosis. Severe ROP was defined as stage ≥3 ROP. Worsening ROP was defined as increased stage of ROP within 8 weeks + 4 days after initiation of sildenafil or matched postmenstrual age.

Results Twenty-three exposed infants and 69 matched controls met the inclusion criteria for the study (mean birth weight, 715 ± 210 g; mean gestational age, 25 ± 1 weeks). The mean postmenstrual age at sildenafil treatment was 42 ± 8 weeks. Exposed infants had more days of respiratory support (mean, 208 ± 101 days vs 102 ± 33 days; $P < .001$). Exposed infants had a higher prevalence of severe ROP (26% [6 of 23] vs 7% [5 of 69]; OR, 6.4; 95% CI, 1.2-32.9; $P = .026$). Five exposed infants and 2 unexposed infants had severe ROP before starting sildenafil and were excluded from the analysis for worsening ROP. The rate of worsening ROP did not differ significantly between exposed infants and unexposed infants ((41% [7 of 17] vs 24% [12 of 51]; OR, 8.4; 95% CI, 0.9-78.6; $P = .061$).

Conclusion Although sildenafil treatment was not statistically significantly associated with worsening of ROP, the raw difference in ROP rate is concerning. Larger studies are warranted to confirm this finding. *(J Pediatr 2018;■■:■■-■■).*

Although survival of extremely premature infants has improved significantly, rates of morbidities, such as bronchopulmonary dysplasia (BPD), have remained stable over the past decade.[1,2] As the pathophysiology has also evolved over time, it is commonly referred to as the "new BPD."[3-6] As opposed to the "old BPD," which was associated with fibrosis and uneven inflation with atelectasis and cystic changes, the "new BPD" is associated with simplification of alveoli and reduced cross-section of the vascular bed, possibly further contributing to pulmonary hypertension. Arjaans et al[7] systematically reviewed and conducted a meta-analysis of 25 studies in the literature on the prevalence of pulmonary hypertension in extremely preterm infants and reported a prevalence of pulmonary hypertension of 2% in infants with no BPD, 6% in those with mild BPD, 12% in those with moderate BPD, and 39% in those with severe BPD. Because pulmonary hypertension in association with BPD contributes significantly to increased risk of morbidity as well as mortality, there are recent data to suggest that treatment of BPD-related pulmonary hypertension may decrease the overall mortality risk.[7-20]

Many centers use sildenafil as an initial drug of choice for the chronic treatment of pulmonary hypertension in these patients with BPD.[16-20] Sildenafil is a phosphodiesterase type 5 inhibitor approved for use for pulmonary hypertension in adults. It reduces cyclic guanosine monophosphate degradation enhancing local endogenous nitric oxide leading to its vasodilating effect. The exacerbation of retinal disease in older adults receiving sildenafil is explained by the accumulation of nitric oxide and cyclic guanosine monophosphate caused by phosphodiesterase type 5 inhibition, which has been hypothesized to exert a proliferative effect on retinal postcapillary venules.[21]

Retinopathy of prematurity (ROP) is a pathological process that occurs only in immature retinal tissue and can alter retinal vascularization, progressing to a tractional retinal detachment.[22,23] Many of the treatment modalities for BPD, such as oxygen, mechanical ventilation, the course of the disease itself and the complications of prematurity, such as sepsis, have been linked to higher incidence and

BPD	Bronchopulmonary dysplasia
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

From the [1]Department of Pediatrics, New York Medical College, Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla; [2]Department of Epidemiology and Community Health, New York Medical College, Valhalla; [3]Department of Pediatrics, Columbia University Medical Center, New York, NY; and [4]Department of Pediatrics, Le Bonheur Hospital, University of Tennessee Health Science Center, Memphis, TN

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greater severity of ROP.[24,25] A provocative case report linked sildenafil use to the development of aggressive ROP in a 26-week preterm infant with a protracted clinical course.[26] The ocular effects of sildenafil in preterm and near-term infants have been elucidated in only 2 retrospective studies and in case reports, showing conflicting results[27-29]; however, Fang et al[27] did not account for BPD status which was different between the cases and control groups and Samiee-Zafarghandy et al[28] analyzed laser surgery rather than accounting for more subtle degrees of ROP worsening. Fawzi et al[30] reported that sildenafil treatment significantly decreased retinal vaso-obliteration and neovascularization in a mouse model of retinopathy induced by hyperoxia. Thus, it is unclear whether previous proposed links with ROP and sildenafil are in fact true associations or proxies for higher-acuity illness of preterm infants. Owing to the limited and conflicting data, we sought to study the influence of the effects of sildenafil on the immature retina on the outcomes of severe (stage >3) ROP and worsening of ROP, because this treatment is increasingly used in this population.

Methods

This is a single-institution retrospective case-control study conducted at the level 4 neonatal intensive care unit (NICU) of a large regional neonatal care referral center with one of the highest acuity levels in the state, admitting more than 650 neonates annually, approximately 200 of whom are very low birth weight (VLBW; <1500 g). The study was approved by the New York Medical College Institutional Review Board Committee.

The study population consisted of VLBW infants with a diagnosis of BPD admitted to the level 4 NICU between January 1, 2006 and December 31, 2012 (**Figure 1**). The exposed (case) group consisted of infants who received sildenafil for pulmonary hypertension in conjunction with an established diagnosis of BPD and were screened for ROP. For each exposed infant, 3 unexposed (controls) were matched based on gestational age (±1 week), birth weight (±100 g), and diagnosis of BPD. Data for exposed and unexposed infants were extracted through the New York State Perinatal Data System, a database including NICU admissions containing information on demographic characteristics, diagnoses, treatments, and procedures for each patient.

We used a modified definition of BPD, a requirement for respiratory or oxygen support at ≥36 weeks postmenstrual age (PMA).[31] Pharmacy records of sildenafil administration were used to identify the exposed group and confirm that controls were unexposed. All infants with a diagnosis of pulmonary hypertension were treated during this period, and the controls did not have a diagnosis or treatment of pulmonary hypertension documented in the records. Sildenafil dosing did not exceed 1 mg/kg/dose 3-4 times daily given enterally. Patients were evaluated for the presence of pulmonary hypertension based on clinical suspicion and not at a predetermined time. pulmonary hypertension was diagnosed using a set of indices including the tricuspid regurgitation Doppler gradient (when reliably present) using the modified Bernoulli equation $4V^2$ (where V is tricuspid regurgitation jet velocity), flattening or

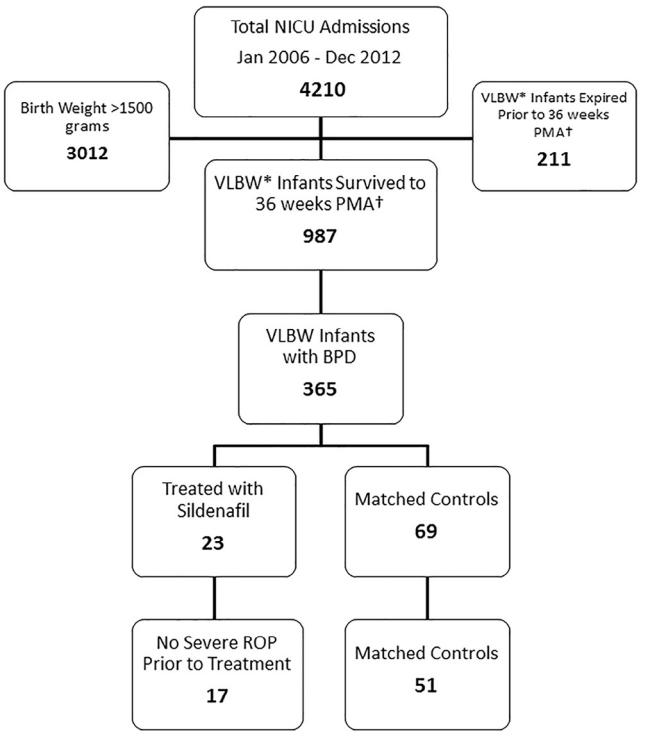

Figure 1. Schematic representation comparing the sildenafil-exposed (case) and -unexposed (control) groups. OR of worsening ROP in cases, 8.4 (95% CI, 0.9-78.6).

posterior bowing of the interventricular septum, right ventricular hypertrophy, pulmonary regurgitation gradient, direction of flow (if a ventricular septal defect or ductus was patent), and gradient across the shunt.[32] The echocardiograms were reviewed by 1 of the 2 author cardiologists and the diagnosis of pulmonary hypertension was confirmed for the purposes of this study. Pulmonary hypertension was graded as severe if estimated pulmonary artery pressure was more than two-thirds of the systemic pressure, as moderate if one-half to two-thirds, and as mild or normal if less than one-half. Only infants with moderate pulmonary hypertension (3 of 23) or severe pulmonary hypertension (20 of 23) were treated with sildenafil.

Data collected included demographic and baseline characteristics, including gestational age, birth weight, mode of delivery, whether inborn or transferred in, Apgar score at 5 minutes of life, and mortality. Additional NICU comorbidities, such as patent ductus arteriosus requiring medical or surgical therapy, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, late-onset sepsis (defined as positive blood culture obtained after the third day of life), receipt of any red blood cell transfusions, and receipt of postnatal steroids, were recorded. Respiratory support days, including invasive and noninvasive ventilation, were documented.

The initial screening of each patient, done by a single ophthalmologist, was based on the American Academy of Pediatrics guidelines for ROP screening.[33] If ROP was identified,

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the patient was referred to a single dedicated pediatric retinal specialist, who determined the frequency of subsequent follow-up examinations and the need for treatment. The records of all eye examinations were reviewed, and the findings were recorded. In the treatment group, the ROP stage and zone of the most recent examination before initiating sildenafil (baseline) and for 8 weeks ± 4 days thereafter were recorded. Unexposed controls were recorded similarly at baseline (PMA of sildenafil initiation for the case to which each was matched) and for 8 weeks ± 4 days thereafter. A follow-up period of 8 weeks ± 4 days was selected because the median PMA at the start of sildenafil treatment was 44 weeks and ROP is known to progress for up to 52 weeks PMA. ROP was classified based on the following international classification: (1) improved/stable: no ROP, ROP regressed, stable immature (for at least 2 examinations), mature; (2) ROP worsening: new ROP at any stage/zone, worsened stage/zone within 8 weeks + 4 days after sildenafil start or matched PMA; (3) severe ROP: stage 3 or higher or need for laser therapy.

The primary outcome was severe ROP, irrespective of when sildenafil was started. The secondary outcome was worsening of ROP within 8 weeks + 4 days after starting sildenafil therapy. Patients with severe ROP at baseline were excluded from the analysis of worsening ROP, because their condition could no longer worsen. Due to the nature of statistical analyses in case-control studies, a patient who had severe ROP at baseline called for exclusion of the entire matched group (1 exposed and 3 unexposed).

Statistical Analyses

Demographic data, clinical characteristics, and outcomes were compared between exposed and unexposed subjects. Conditional logistic regression was used for all analyses comparing exposed infants with unexposed controls to properly account for the 3:1-matched study design.[34,35] All other analyses were done using univariate logistic regression. Because sildenafil is a rare treatment, we maximized statistical power with our given population by using a case-control design and relying primarily on univariate modeling. We did not use propensity score matching, because logistic regression with a multitude of covariates is required to assign propensity scores, and we lacked a sufficient he number of exposed infants needed for this step.[36] A P value <.05 was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Exposed subjects (n = 23) and unexposed controls (n = 69), all with BPD defined as the need for respiratory support at ≥36 weeks PMA, were matched for birth weight (mean, 711 ± 220 g vs 716 ± 208 g) and gestational age (mean, 25 ± 1.6 weeks vs 25 ± 1.4 weeks) (**Figure 1**). Among exposed infants, mean PMA at the start of sildenafil was 42 ± 8 weeks (median, 44 weeks; range, 26-63 weeks). Race/ethnicity was available only in 57% of cases, and thus this variable was not included in our analysis.

Table I presents detailed demographic and morbidity information by sildenafil treatment. The exposed group had higher rates of late-onset sepsis compared with controls. Whether sepsis contributed to the development of pulmonary hypertension is unclear. Even though BPD was present in all infants in our study, the exposed group required a longer duration of respiratory support compared with controls (mean, 208 ± 101 days vs 102 ± 33 days; $P < .001$). Infants with severe ROP had lower birth weight than those without (mean, 583 ± 104 g vs 733 ± 215 g), but otherwise had similar demographic characteristics and morbidities (**Table II**). Irrespective of when sildenafil was initiated, the overall rate of severe ROP was higher in the exposed group (26% [6 of 23] vs 7% [5 of 69]; OR, 6.4; 95% CI, 1.2-32.9; $P = .026$). However, 5 exposed subjects and 2 unexposed controls had severe ROP at baseline (before starting sildenafil or the corresponding PMA).

We excluded all matched groups with any subjects with baseline severe ROP, to accurately analyze the association between sildenafil and worsening ROP. A total of 17 exposed subjects and 51 matched unexposed controls were analyzed for worsening ROP. The 17 exposed subjects included in this analysis started sildenafil at mean PMA of 40 ± 7 weeks, (median, 42 weeks; range, 26-49 weeks). There was no significant difference in the rate of worsening ROP between cases and

Table I. Demographic data and morbidities in cases and controls

Characteristics	Sildenafil-treated (cases; n = 23)	Not sildenafil-treated (controls; n = 69)	*P* value*
Birth weight, g, mean ± SD; median (range)	711 ± 220; 640 (430-1245)	716 ± 208; 630 (450-1310)	.570
Gestational age, wk, mean ± SD; median (range)	25 ± 1; 25 (23-29)	25 ± 1; 25 (23-29)	.994
Cesarean delivery, n (%)	14 (61)	45 (65)	.686
Male sex, n (%)	14 (61)	38 (55)	.647
Five-min Apgar score <7, n (%)	10 (45)	29 (43)	.871
Total respiratory support days, mean ± SD; median (range)	208 ± 101; 214 (50-389)	102 ± 33; 100 (33-224)	<.001
Receipt of postnatal steroids, n (%)	11 (48)	19 (28)	.082
Patent ductus arteriosus requiring treatment, n (%)	13 (57)	47 (68)	.355
Grade III or IV intraventricular hemorrhage, n (%)	4 (17)	9 (13)	.592
Necrotizing enterocolitis, n (%)	5 (22)	10 (14)	.374
Receipt of red blood cell transfusion, n (%)	19 (83)	60 (87)	.592
Late-onset sepsis, n (%)	10 (43)	12 (17)	.022
Survived to discharge from NICU, n (%)	20 (87)	68 (99)	.057

*P value from conditional logistic regression.

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Table II. Demographic data and morbidities by ROP status

Characteristics	Severe ROP (n = 11)	No severe ROP (n = 81)	*P* value*
Birth weight, g, mean ± SD; median (range)	583 ± 104; 602 (430-750)	733 ± 215; 640 (460-1310)	.040
Gestational age, wk, mean ± SD; median (range)	25 ± 1; 25 (23-26)	25 ± 2; 26 (23-29)	.193
Cesarean delivery, n (%)	9 (82)	50 (62)	.208
Male sex, n (%)	6 (55)	46 (57)	.888
Five-min Apgar score <7, n (%)	6 (55)	33 (42)	.427
Total respiratory support days, mean ± SD; median (range)	161 ± 102; 115 (64-351)	124 ± 68; 105 (33-389)	.127
Receipt of postnatal steroids, n (%)	2 (18)	28 (35)	.289
Patent ductus arteriosus requiring treatment, n (%)	8 (73)	52 (64)	.579
Grade III or IV intraventricular hemorrhage, n (%)	2 (18)	11 (14)	.682
Necrotizing enterocolitis, n (%)	3 (27)	12 (15)	.303
Receipt of red blood cell transfusion, n (%)	8 (73)	71 (88)	.196
Late-onset sepsis, n (%)	3 (27)	19 (23)	.781
Survived to discharge from NICU, n (%)	11 (100)	77 (95)	—

**P* value from univariate logistic regression.

controls (41% [7 of 17] vs 24% [12 of 51]; OR, 8.4; 95% CI, 0.9-78.6; $P = .061$). There was no difference in total respiratory support days between the subjects with worsening ROP and those without worsening ROP (Figure 2).

Discussion

This study investigating the association between sildenafil treatment and worsening ROP found that although infants treated with sildenafil had a higher prevalence of severe ROP than those without sildenafil, they did not have a significantly higher rate of worsening ROP. The difference in ROP rate between sildenafil-exposed and -unexposed infants remains a concern, and larger studies may be needed to evaluate this association more thoroughly. As expected, the infants with BPD and pulmonary hypertension treated with sildenafil had longer duration of respiratory support and a higher rate of late-onset sepsis, suggesting a more severe clinical course.[37-39] Sildenafil is used for the smallest, sickest infants with pulmonary hypertension, a population that is already associated with higher morbidity and a greater number of ventilator-days, as observed in the present study.

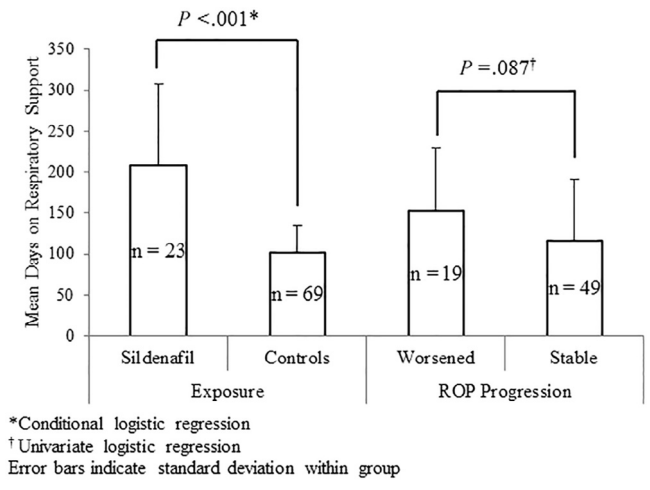

Figure 2. Mean respiratory days by sildenafil therapy and worsening ROP. *Conditional logistic regression. †Univariate logistic regression. Error bars indicate SD within groups.

In a 12-week open-label phase III trial to assess the ocular effects of chronic sildenafil dosing in 277 adults with pulmonary hypertension, Wirostko et al[21] did not find a deleterious effect on any of the vision and intraocular variables studied. Several case series have reported sildenafil use in preterm infants and have evaluated ocular side effects, with few suggesting worsening and others showing no change.[26-29] In a retrospective observational study that included 22 term and near-term neonates treated with sildenafil, Kehat et al[29] demonstrated that ocular complications were not directly linked to sildenafil use. In contrast, the present study included only VLBW infants with BPD, showing the impact of sildenafil on ROP in a high-risk neonate population. Fang et al[27] studied 17 preterm neonates under 30 weeks treated with sildenafil and found no increase in ROP. Our patients were younger in gestational age and were matched for BPD status. In addition, for our focus on worsening ROP, we excluded infants with severe ROP at the start of sildenafil treatment. In a large retrospective study with data obtained from electronic documentation of clinical care, Samiee-Zafarghandy et al[28] did not observe an association between severe ROP and sildenafil exposure. Their patients had a higher gestational age and birth weight and a shorter duration of sildenafil therapy, and were not matched for BPD status. In addition, the ocular effects of sildenafil were assessed not by actual eye examinations, but rather by the documentation of laser therapy, thus capturing only the severe forms of ROP.

The present study has a number of limitations. Because sildenafil is a rare treatment, research on infant sildenafil use lends itself to undersized comparison groups, providing a barrier to multivariate statistical modeling. However, we maximized statistical power with our given population by assigning 3 unexposed controls for each exposed subject, while equalizing infant acuity by matching on gestational age, birth weight, and BPD diagnosis. Regardless, the width of our 95% CIs suggest that the analysis of worsening ROP was underpowered, leaving us unable to detect marginal effects.[40,41] Another limitation is that, consistent with American Heart

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Association and American Thoracic Society recommendations, the median PMA at the start of sildenafil therapy was 44 weeks in this population.[42] Thus, the age at start of sildenafil is advanced and might not reflect the true preterm population at risk for the potential ocular side effects of sildenafil if started earlier. However, a majority of our patients did not have fully developed retinas, and 17 of the 23 treated infants were still at risk of worsening ROP at the time of sildenafil treatment. The lack of data on patient race and ethnicity is a limitation, given that rates of ROP as well as medication side effects can vary by race and ethnicity.[43] We were unable to include race and ethnicity data because 43% of our subjects were missing this information. The potential impacts of race and ethnicity on associations with sildenafil use should be addressed in future studies.

Our study has a number of strengths. We studied only VLBW infants, so our entire cohort was at an already greater risk of developing ROP compared with the term or near-term infants included in other studies. We also factored temporal order into our analysis by studying worsening ROP in relation to the start of sildenafil treatment.

Although sildenafil treatment was not significantly associated with worsening ROP, the raw difference in rates between the 2 groups remains a concern. The use of medications that exert not only an immediate vasodilatory effect but also a long-term modifying angiogenesis effect should be done with caution, close monitoring, and consistent follow-up in these vulnerable patients. As suggested in the American Heart Association and American Thoracic Society guidelines, delaying the use of sildenafil after maturation of the retinal vasculature is optimal.[42] Establishment of a national database of BPD-associated pulmonary hypertension, as well as a prospective multicenter study of VLBW infants correlating the timing and use of sildenafil and ocular changes may shed further light on the topic. ■

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Reprint requests: Usha Krishnan, MD, DM, FAHA, Division of Pediatric Cardiology, CHN 2N # 255, 3959 Broadway, New York, NY 10032. E-mail: usk1@cumc.columbia.edu

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