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

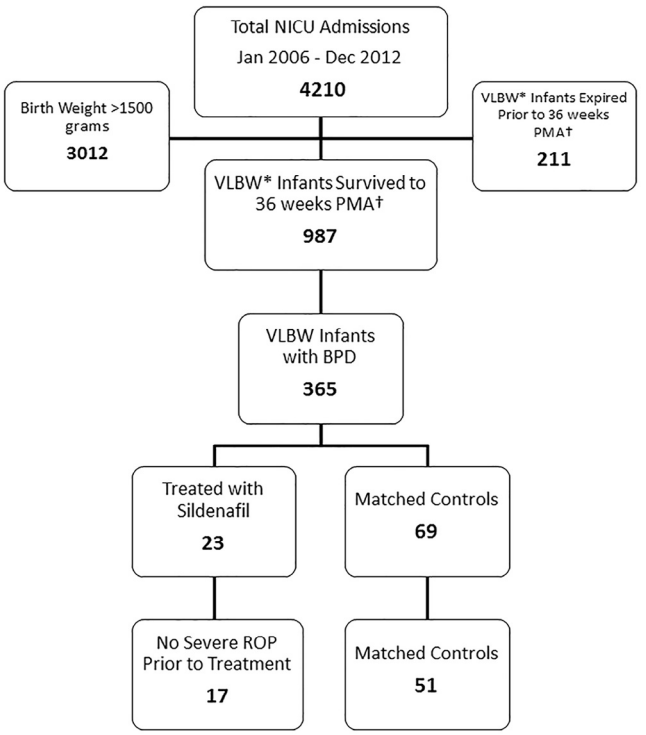

Figure 1. Schematic representation comparing the sildenafil-exposed (case) and -unexposed (control) groups. OR of worsening ROP in cases, 8.4 (95% CI, 0.9-78.6).

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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