

Possible Role of Sildenafil Citrate in the Recurrence of Neovascularization in Laser-regressed Aggressive Posterior ROP

CHAITRA JAYADEV,[#] PHANIBHUSHAN RAMASASTRY, ALIA GUL AND ANAND VINEKAR

From Departments of Pediatric Retina, Narayana Nethralaya Institute ; and [#]Neonatology, Columbia Asia Referral Hospital, Bangalore, India.

*Correspondence to: Dr Anand Vinekar,
Department of Pediatric Retina, Narayana
Nethralaya Eye Institute, 121/C, 1st R
Block, Rajajinagar, Bangalore 560010,
India. anandvinekar@yahoo.com,
Received: June 25, 2015;
Initial review: August 20, 2015;
Accepted: September 14, 2016.*

Background: Systemic diseases and their treatment influence aggressive posterior retinopathy of prematurity. **Case characteristics:** A premature infant with aggressive posterior retinopathy of prematurity underwent laser treatment with a favourable outcome. She was started on oral sildenafil citrate for pulmonary hypertension. Ten days later she developed neovascularization within the lasered retina. **Intervention/Outcome:** Considering the possible role of sildenafil in this unusual development, the drug was withdrawn resulting in regression of the neovascularization. **Message:** The clinician should be aware of this retinal adverse effect of sildenafil in neonates with aggressive posterior retinopathy of prematurity.

Keywords: Laser photocoagulation, Neovascularization, Retinopathy of prematurity.

Aggressive posterior retinopathy of prematurity (APROP) is a rapidly progressive retinopathy of prematurity (ROP) that requires laser photocoagulation, often in two or more sessions to treat the associated flat neovascularization [1,2]. Extensive and thorough confluent burns show favorable outcomes in a good percentage of infants [3]. Associated systemic diseases, especially hematological etiologies, play an important role in APROP [4]. Sildenafil acetate has been used in neonates with persistent pulmonary hypertension due to its selective vasodilator action [5]. The drug is associated with several transitory and reversible adverse ocular effects in adults, but its role in neonates has been controversial [6-9].

We report recurrence of retinal neovascularization (NVE) in a premature infant after the initiation of oral sildenafil despite prior complete regression following laser treatment for APROP.

CASE REPORT

A premature girl born with a birthweight of 700 g at 24.5 weeks of gestation required ventilation from birth for respiratory distress syndrome. Attempts to wean her off the ventilator resulted in recurrent apnea. During her admission in the neonatal intensive care unit, she was treated for bacterial (*Klebsiella spp.*) sepsis, pulmonary hemorrhage, and underwent surgical ligation for patent ductus arteriosus. By the end of the second month, her oxygen need had reduced to 30-40%, but she still needed intermittent continuous positive airway pressure (CPAP).

Retinopathy of prematurity screening and weekly Retcam documentation (Clarity MSI, CA, USA) was performed starting at the third week of life owing to her very low birth weight, according to the current national screening guidelines. At 28.4 weeks post-menstrual age (PMA), APROP was diagnosed and the infant underwent laser photocoagulation. At 30.3 weeks, supplement fill-in laser was given to cover the ischemic bed following retraction of the flat neovascularization complex using the method previously described [1,2]. Both eyes showed good regression of the disease, absence of any skip areas or ischemic retinal beds, and obliteration of the neovascular complex along with complete resolution of the plus disease (**Web Fig. 1**).

However, secondary to the chronic lung disease, she developed moderate to severe persistent pulmonary hypertension of newborn. The neonatologist initiated oral sildenafil acetate at a dose of 0.8 mg/kg/day in three divided doses on the 33rd PMA week, after a trial of hydrochlorothiazide failed to improve the chronic lung disease. Twelve days after initiating sildenafil, an area of 'new neovascularization' was noted in both eyes in the temporal quadrants within the lasered retinal bed (**Web Fig. 2**). This area had bled in the left eye throughout the extent of the fibrous band. There was neither recurrence of plus disease at this stage in either eye, nor any new 'skip' areas that needed laser supplement.

Considering the possible role of sildenafil in this unusual development, it was decided to withdraw the drug after having given it for 20 days. The oxygen requirements

also stabilized by this time to 26 to 30% and the infant could be weaned-off CPAP, requiring only hood oxygen at 0.5 litres/minute.

Within 12 days of sildenafil cessation (37.4 weeks PMA), the vascular component of the fibrovascular band showed reduction in height and vascularity (*Web Fig. 3*). No additional laser treatment was required thereafter. Over the next three weeks, there was continual improvement in the appearance of the band and only a thin fibrous chord remained, which persisted until the last follow up at 7 months of corrected age

DISCUSSION

Sildenafil acetate induces vasodilation by enhancing the smooth muscle relaxant effects of nitric oxide by inhibition of phosphodiesterase type 5 (PDE5) [4]. In ROP, retinal hyperperfusion has been linked to the local release of growth factors and free radical production. In addition, nitric oxide (NO) and cGMP accumulation caused by PDE5 inhibition has been proposed to exert a proliferative effect on retinal post-capillary venules [5,6]. While Marsh, *et al.* [6] reported an increase in treatable ROP coinciding with the use of sildenafil, Pierce, *et al.* [7] attributed it to other confounding risk factors such as inhaled NO, which is also a vasodilator.

This report documents 'new neovascular growth' that developed after the initiation of oral sildenafil in a very-low birth weight premature infant who had shown complete resolution of APROP following laser. One of the hallmarks of APROP is the presence of intra-retinal shunts and flat neovascularization, which needs laser treatment, often in multiple sessions, to address the ischemic retinal bed underlying the flat neovascularization [1,2]. It is likely; however, that the intra-retinal shunts may take longer to resolve and lie dormant and subclinical before complete resolution takes place, which can be monitored on fundus fluorescein angiography [10]. It is probable that these dormant, yet vascularly 'active' intra-retinal shunts undergo dilatation and proliferation secondary to sildenafil. The reduction in the caliber and tortuosity of these dilated vessels after withdrawal of the drug in our case, further strengthens the theory.

Although it may be argued that APROP is known to recur even after initial 'resolution' of the disease, this recurrence is typically seen in the form of plus disease and progression to extraretinal fibrovascular proliferation and retinal detachment [1,2]. Furthermore, recurrent APROP would progress to retinal detachment without further treatment [1]. In our case, the only 'recurrence' was the neovascular complex and hemorrhage from it, without worsening of the plus disease or progression of the APROP. Furthermore, it spontaneously regressed after

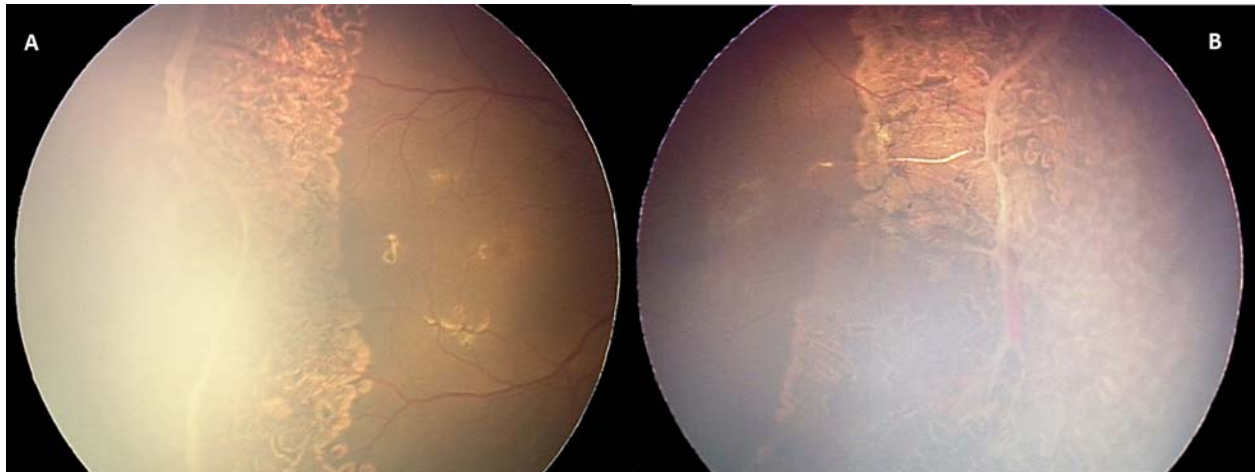
withdrawal of the drug implicating the inciting influence of sildenafil.

Despite an absence of confounding systemic factors that may have contributed to the worsening of disease, sildenafil cannot be solely implicated without definite evidence. While larger studies may provide that evidence, it is imperative to explore alternative treatments for this highly vulnerable population. Until then, the neonatologist and treating ophthalmologist must be aware of this possible retinal adverse effect of sildenafil, which can appear even after a seemingly well treated and resolved APROP.

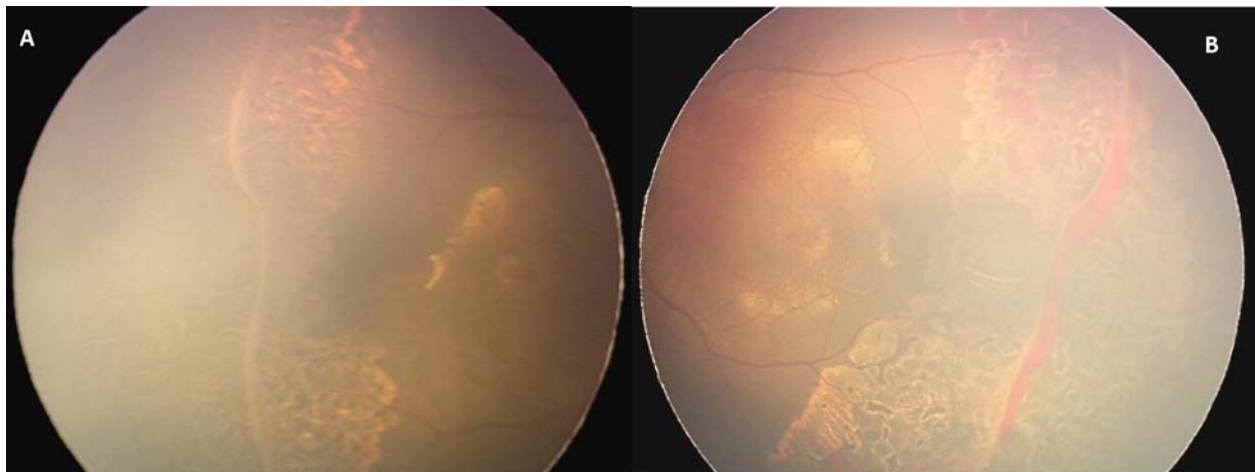
Contributors: All authors contributed equally to the manuscript.
Funding: None; *Competing interests:* None stated.

REFERENCES

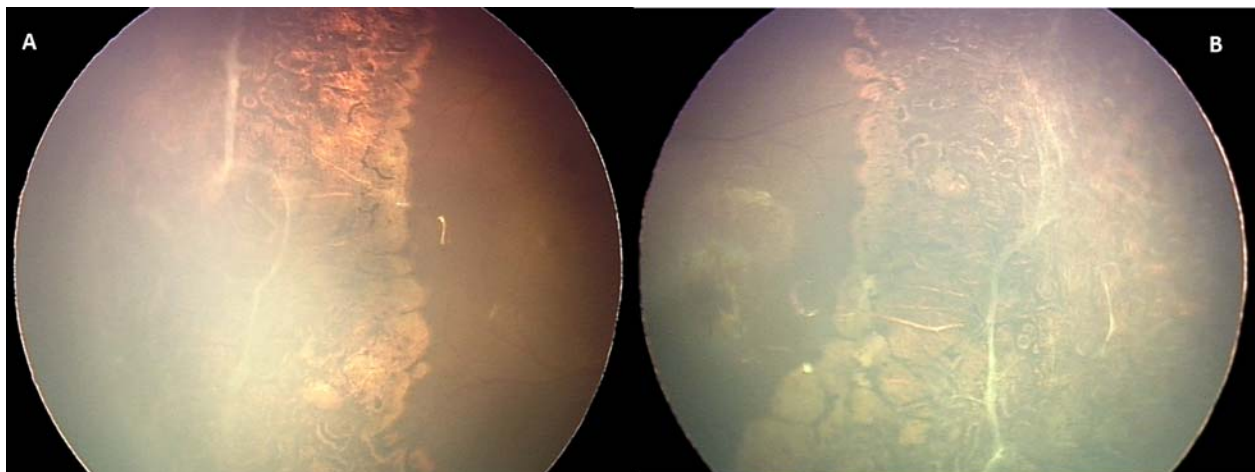
1. Vinekar A, Trese MT, Capone A Jr. Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: Impact on treatment approach. *Am J Ophthalmol.* 2008;145:548-55.
2. Vinekar A, Jayadev C, Mangalesh S, Kumar AK, Bauer N, Capone A Jr, *et al.* Comparing the outcome of single versus multiple session laser photocoagulation of flat neovascularization in zone 1 aggressive posterior retinopathy of prematurity: A prospective randomized study. *Retino.* 2015 ;35:2130-6.
3. Sanghi G, Dogra MR, Das P, Vinekar A, Gupta A, Dutta S. Aggressive posterior retinopathy of prematurity in Asian Indian babies: Spectrum of disease and outcome after laser treatment. *Retina.* 2009;29:1335-9.
4. Vinekar A, Hegde K, Gilbert C, Braganza S, Pradeep M, Shetty R, *et al.* Do platelets have a role in the pathogenesis of aggressive posterior of prematurity. *Retina.* 2010; 20:S20-3.
5. Grunwald JE, Siu KK, Jacob SS, Dupont J. Effect of sildenafil citrate (Viagra) on the ocular circulation. *Am J Ophthalmol.* 2001;131:751-5.
6. Marsh CS, Marden B, Newson R. Severe retinopathy of prematurity (ROP) in a premature baby treated with sildenafil acetate (Viagra) for pulmonary hypertension. *Br J Ophthalmol.* 2004;88:306-7.
7. Pierce CM, Petros AJ, Fielder AR. No evidence for severe retinopathy of prematurity following sildenafil. *Br J Ophthalmol.* 2005;89:250.
8. Fawzi AA, Chou JC, Kim GA, Rollins SD, Taylor JM, Farrow KN. Sildenafil attenuates vaso-obliteration and neovascularization in a mouse model of retinopathy of prematurity. *Invest Ophthalmol Vis Sci.* 2014;55:1493-501.
9. Fang AY, Guy KJ, König K. The effect of sildenafil on retinopathy of prematurity in very preterm infants. *J Perinatol.* 2013;33:218-21.
10. Klufas MA, Patel SN, Ryan MC, Patel Gupta M, Jonas KE, Ostmo S, *et al.* Influence of fluorescein angiography on the diagnosis and management of retinopathy of prematurity. *Ophthalmology.* 2015;122:1601-8.



Web Fig.1 The temporal quadrants of the right eye (A) and left eye (B) respectively showing healed laser scars with complete resolution of plus disease.,



Web Fig. 2 Ten days after initiating oral sildenafil, both right eye (A) and left eye (B) developed thickened vascular bands with fibrous components within the lasered beds in the temporal quadrants.



Web Fig. 3 Twelve days after cessation of sildenafil, the 'vascular' components of bands were 'quieter' with a reduction in the height and width of the vascular components in the right eye (A) and left eye (B).