

Current Management of Retinopathy of Prematurity: The Good, the Bad and the Ugly

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Since Terry's [1] histopathologic description of retrolental fibroplasia – subsequently renamed retinopathy of prematurity (ROP) – neonatologists and ophthalmologists have struggled to care for afflicted infants. The subsequent 7 decades have witnessed encouraging advances in both the understanding and treatment of ROP, but hundreds of babies are still blinded each year. This editorial aims to discuss recent breakthroughs, persistent challenges, and the effects of the deteriorating medicolegal climate on the screening and treatment of babies.

The CRYO-ROP trial [2] showed that timely ablation of the avascular peripheral retina decreases the incidence of an unfavorable anatomical outcome by 40%. The introduction of the indirect laser photocoagulator prompted most physicians to convert to retinal photocoagulation, but the failure rate remained unacceptably high. Since the neovascular drive in ROP eyes with stage 3 disease has been closely correlated with intraocular VEGF levels, some investigators successfully treated small numbers of threshold ROP eyes with intravitreal bevacizumab. The good news concerns the recently completed BEAT-ROP [3] trial which showed that eyes with zone 1 threshold disease fared far better when treated with bevacizumab than laser and that zone 2 eyes fared comparably with both treatments. Remarkably, most eyes required only a single bevacizumab injection.

What the study could not show because of its short follow-up period are the visual results. ROP eyes are known to suffer from decreased visual acuity, visual field constriction and high myopia. Laser photocoagulation may not exacerbate visual field loss [4]. So this may be attributed directly to ROP. Would bevacizumab improve peripheral visual field perception by facilitating normal retinal vascularization? Or would bevacizumab, with its effect on apoptosis, hasten damage to peripheral neurosensory retina already suffering from chronic ischemia? Some authors worry that repeated anti-VEGF therapy for exudative age-related macular degeneration may accelerate RPE loss.

Despite these unanswered questions, the encouraging results of the BEAT-ROP trial will likely convince treating physicians to shift from laser photocoagulation to intravitreal bevacizumab. The standardized injection protocol within the BEAT-ROP study appeared safe but the increasing use of intravitreal bevacizumab will create its own set of technical challenges and surgical complications. Since neonatal eyes are considerably smaller than adult eyes (diameter: 17 mm vs. 24 mm), the surgical safety window between the crystalline lens and peripheral retina shrinks significantly. Whereas non-retinal ophthalmologists may comfortably perform intravitreal injections in adult eyes, injections in neonates must be approached with significantly more care.

Excessive oxygen administration is a well known cause of ROP [5]. For decades neonatologists addressed this by carefully restricting oxygen administration to premature infants. Despite this well-intentioned strategy, improving neonatal survival rates led to an increasing number of ROP cases without reducing the number of blind babies [6].

Since adequate oxygen is necessary for neonatal growth and development neonatologists worried that the ROP-mandated low oxygen delivery was compromising babies' growth. The STOP-ROP study [7] showed that higher oxygen delivery (96-99% vs. 89-94%)

to babies with early ROP promoted overall growth and development without adversely affecting the course of ROP. Although the study established the safety of higher oxygen delivery it did not change the course of the ROP.

Two neonatal periods are critical to the development of ROP. Immediately after birth, the immature retina experiences a relative hyperoxia as pulmonary respiration with supplemental oxygen acutely raises retinal oxygen saturation far above levels experienced *in utero*. High oxygen tension damages immature retinal capillary endothelial cells, thereby preventing complete vascularization. Following this initial period, neonatologists carefully restrict oxygen to lower the likelihood of ROP development. The avascular peripheral retina remains chronically hypoxic during this period, leading to compensatory VEGF synthesis and pathologic neovascularization.

In his recent editorial entitled "How to Prevent Retinopathy of Prematurity: a hypothesis" Stefansson [8] proposed non-invasive, *in vivo* retinal oxygen monitoring to optimize tissue rather than blood saturations. Retinal oxygen levels could then be optimally regulated to ensure normal development by adjusting 2 factors:

1. Respiratory/ventilator parameters including the concentration of inspired Oxygen.
2. Incident light exposure to the retina. Since dark adapted retina is metabolically more active, the amount of incident illumination would determine the metabolic rate and, therefore, oxygen consumption.

Though successful implementation of his plan would be difficult, particularly during the first hours after birth when frenetic clinical and testing activity focuses on saving babies' lives, it offers a promising new avenue of research.

The contentious medicolegal climate surrounding ROP screening and treatment has created an ugly problem. The number of malpractice cases is relatively small - the Ophthalmic Mutual Insurance Company, which insures 35% of ophthalmologists, closed only 12 ROP claims between 1989 and 2009 [9] - but each lawsuit exposes physicians to potentially multi-million dollar judgments. This has dissuaded many physicians from performing screening exams and treatments.

A recent survey discovered that one fifth of ophthalmologists

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performing ROP screening planned to quit soon [10]. Some urban areas cannot find physicians willing to treat neonates. The author once accepted the life-flight transfer of a baby with “threshold ROP”; the 300 mile flight cost over \$50,000. Fortunately, the baby had only stage 1 disease, so he was transferred home for another \$50,000. These are some of the exorbitant, hidden costs of the ROP crisis.

Most lawsuits allege a missed diagnosis, either due to delay in initial screening or failure to perform follow-up examinations [11]. Handoffs occurring when infants are transferred between hospitals or discharged from the hospital are moments of particular high risk for loss of continuity of care. The author worked closely with a NICU case manager to regularly communicate with the NICU staff regarding all babies, and maintain a ROP exam schedule spreadsheet that was updated immediately after each week’s exams and shared through e-mail. This system never led to a breakdown in continuity of care. A carefully constructed fail-safe system with vigilant attention to detail will work, but many institutions and practices have not devoted the time and attention to successfully implement such practices.

So what can these trends tell us about the future of ROP care? Clearly there exists tremendous opportunity for decreasing blindness and allowing physicians to deliver care without fear of financial ruin. Physicians should, and will, switch from laser retinopexy to intravitreal bevacizumab. In addition to the improved efficacy, particularly for zone 1 disease, treatment consumes less time and minimizes trauma to the infants. To manage the apnea and bradycardia that frequently accompanied laser photoablation, the author’s NICU would routinely intubate and paralyze babies; we now take no special medical precautions for bevacizumab injections.

Hospitals should employ ophthalmologists specifically for ROP screening and treatment. Liability insurance can be provided by the hospital, thereby minimizing the physician’s exposure to malpractice claims. Physicians should meet with NICU coordinators to create a fail-safe tracking system to assure initial screenings, follow-up exams and post-discharge care.

Preventing the development of ROP will be the most difficult piece

of the puzzle. Research should focus more on the initial hours of life when Irreversible capillary damage probably occurs. Can we keep tissue oxygen?

Tension low without compromising survival? Will Stefansson’s non-invasive Oxygen monitor enable better oxygen regulation?

We certainly have the ability to nearly eradicate blindness from ROP, but let’s hope we also have the courage to do all that is necessary.

References

1. Terry TL (1942) Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report. *Am J Ophthalmol* 25: 203-204.
2. Cryotherapy for Retinopathy of Prematurity Cooperative Group (1990) Multicenter trial of cryotherapy for retinopathy of prematurity. 3 month outcome. *Arch Ophthalmol* 108: 195-204.
3. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group (2011) Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 364: 603-615.
4. Quinn GE, Dobson V, Hardy RJ, Tung B, Palmer EA, et al. (2011) Visual field extent at 6 years of age in children who had high-risk prethreshold retinopathy of prematurity. *Arch Ophthalmol* 129: 127-132.
5. Kinsey VE (1956) Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. *AMA Arch Ophthalmol* 56: 481-543.
6. Phelps DL (1981) Retinopathy of prematurity: an estimate of vision loss in the United States - 1979. *Pediatrics* 67: 924-926.
7. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP): a randomized, controlled trial. I. Primary outcomes. (2000) *Pediatrics* 105: 295-310.
8. Stefansson E (2011) How to prevent retinopathy of prematurity: a hypothesis. *Acta Ophthalmol* 89: 3-4.
9. Day S, Menke AM, Abbott RL (2009) Retinopathy of prematurity malpractice claims: the Ophthalmic Mutual Insurance Company experience. *Arch Ophthalmol* 127: 794-798.
10. Survey: physicians being driven away from ROP treatment. *Ocular Surgery News Web site*. <http://www.osnsupersite.com/view.asp?rID=18018>. Accessed May 15, 2008.
11. Reynolds JD (2007) Malpractice and the quality of care in retinopathy of prematurity (an American Ophthalmological Society Thesis). *Trans Am Ophthalmol Soc* 105: 461-480.