Safety of Retinopathy of Prematurity Examination and Imaging in Premature Infants

Kelly C. Wade, MD, PhD, MSCE[1], Maxwell Pistilli, MS[2], Agnieshka Baumritter, MS[3], Karen Karp, BSN[3], Alice Gong, MD[4], Alex R. Kemper, MD, MPH, MS[5], Gui-Shuang Ying, PhD[2], and Graham Quinn, MD, MSCE[2,3], on behalf of the e-Retinopathy of Prematurity Study Cooperative Group*

Objectives To describe adverse events (AEs) and noteworthy clinical or ocular findings associated with retinopathy of prematurity (ROP) evaluation procedures.

Study design Descriptive analysis of predefined AEs and noteworthy findings reported in a prospective observational cohort study of infants <1251 g birth weight who had ROP study visits consisting of both binocular indirect ophthalmoscopy (BIO) and digital retinal imaging. We compared infant characteristics during ROP visits with and without AEs. We compared respiratory support, nutrition, and number of apnea, bradycardia, or hypoxia events 12 hours before and after ROP visits.

Results A total of 1257 infants, mean birth weight 802 g, had 4263 BIO and 4048 imaging sessions (total 8311 procedures). No serious AEs were related to ROP visits. Sixty-five AEs were reported among 61 infants for an AE rate of 4.9% infants (61/1257) or 0.8% total procedures (65/8311 BIO + imaging). Most AEs were due to apnea, bradycardia, and/or hypoxia (68%), tachycardia (16%), or emesis (8%). At ROP visit, infants with AEs, compared with those without, were more likely to be on mechanical ventilation (26% vs 12%, $P = .04$) even after adjustment for weight and postmenstrual age. Noteworthy clinical findings were reported during 8% BIO and 15% imaging examinations. Respiratory and nutrition support were not significantly different before and after ROP evaluations.

Conclusions Retinal imaging by nonphysicians combined with BIO was safe. Noteworthy clinical findings occurred during both procedures. Ventilator support was a risk factor for AEs. Monitoring rates of AEs and noteworthy findings are important to the safe implementation of ROP imaging protocols. *(J Pediatr 2015;167:994-1000)*.

Trial registration Clinicaltrials.gov: NCT01264276.

Retinopathy of prematurity (ROP), a developmental vascular proliferative disease of the retina in premature infants, is a leading potentially avoidable cause of childhood blindness.[1] To assure timely treatment, premature infants with birth weight (BW) <1500 g or gestational age (GA) of 30 weeks or less typically have binocular indirect ophthalmoscopy (BIO) serially every 1-3 weeks starting at 30-32 weeks postmenstrual age (PMA) until the infant is either no longer at risk for ROP or has developed significant enough ROP to warrant treatment.[2] Digital retinal imaging (imaging) with a wide-angle camera may be a suitable alternative for BIO.[3]

Examination of premature infants using BIO can elicit pain responses, can lead to changes in heart rate, blood pressure, and oxygen saturation, and has been associated with apnea and bradycardia events during and after the examination.[2,4-8] These changes may be due to a wide variety of causes including the oculocardiac reflex, systemic absorption of alpha-adrenergic and anticholinergic medications administered for mydriasis, scleral depression, application of the speculum to eyelid, bright lights, and nonspecific pain or stress.[2,4-8] Serious adverse events (SAEs) including necrotizing enterocolitis and cardiopulmonary arrest have been reported.[9-11]

AE	Adverse event
BIO	Binocular indirect ophthalmoscopy
BW	Birth weight
CPAP	Continuous positive airway pressure
e-ROP	Telemedicine Approaches to Evaluating Acute Phase-ROP
GA	Gestational age
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
SAE	Serious adverse event

From the [1]Department of Pediatrics, Children's Hospital of Philadelphia; [2]Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Perelman School of Medicine; [3]Division of Pediatric Ophthalmology, Children's Hospital of Philadelphia, Philadelphia, PA; [4]Department of Pediatrics, University of Texas, San Antonio, TX; and [5]Duke Clinical Research Institute, Durham, NC

*List of members of the e-ROP Study Cooperative Group members are available at www.jpeds.com (**Appendix**).

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Digital retinal imaging exposes the infant to the similar mydriatic medications, eye manipulations, and bright light exposure. Small studies comparing imaging and BIO have demonstrated similar pain responses and physiologic changes during both procedures.[8,12] Little is known about the frequency or severity of adverse events (AEs) and noteworthy clinical or ocular findings that occur during imaging.

We sought to evaluate the safety of ROP evaluation procedures as part of the large observational Telemedicine Approaches to Evaluating Acute Phase-ROP (e-ROP) study.[13,14] During ROP study visits, infants had both BIO by ophthalmologists and imaging by nonphysicians on the same day. This safety analysis describes the AEs and noteworthy clinical and ocular findings reported during or shortly thereafter ROP study visits.

Methods

Between May 2011 and October 2013, the e-ROP study enrolled 1284 infants with BW <1251 g of whom 1257 infants had ROP evaluations at 1 of 12 US or a Canadian neonatal intensive care units (NICUs) (Clinicaltrials.gov: NCT01264276).[13,14] Exclusion criteria were the presence of major ocular abnormalities, significant media opacity precluding visualization of the retina, or treated or known regressing ROP at time of admission into an e-ROP clinical center. There were no exclusions for other congenital anomalies or level of illness if infant was expected to have ROP screening procedures. The study protocol and informed consent processes were approved by the institutional review board of all participating centers, with written informed consent.

ROP Study Visit Definitions and Staff Training

ROP evaluations, referred to as ROP study visits, included both BIO by a study certified ophthalmologist and imaging by a study certified nonphysician imager.[13] Imagers had a variety of professional backgrounds that included NICU nurses and nurse practitioners (68%), ophthalmic photographers and technologists (16%), and individuals with no clinical background (16%).[13] ROP study visits typically began at 32 weeks PMA and continued every 1-2 weeks according to the local center standard of care. Imaging and BIO took place on the same day, typically within an hour of each other. The order in which imaging or BIO occurred varied. We determined which procedure was performed first using the recorded start time of each procedure; procedure duration was not reported. Ophthalmologists and imagers were masked to each other's ROP findings. Only BIO findings were used for clinical care, and the examining ophthalmologist determined follow-up. Rarely, study visits (44 visits, 1%) were performed at 30-31 weeks PMA, and for these visits imaging was deferred. Imaging also could be deferred for infants who were transferred off the unit at time of imaging, considered too sick by study personnel, or by parent or nursing request.

Key Safety Measures and Definitions of AEs and Noteworthy Findings

To enhance the safety of ROP procedures, ophthalmologists, imagers, and study coordinators were trained and certified in the general practices of baby-centered care during procedures. Specifically, they were instructed to: (1) coordinate with bedside nursing staff throughout procedures with attention given to the timing of feeds, infant positioning, temperature regulation, and the security of respiratory and intravenous equipment; (2) adhere to hand hygiene and infection control practices of the NICU; (3) minimize pain with anesthetic ophthalmic drops, and sucrose solutions per local center standard of care; and (4) minimize infant stress by swaddling and limiting time of procedures, specifically camera contact and speculum time.

At each ROP study visit, the following infant characteristics were reported: weight, PMA, postnatal age, respiratory support, enteral nutrition support, and number of reported events of prematurity during the previous 12 hours. Respiratory support categories included: (1) mechanical ventilator; (2) continuous positive airway pressure (CPAP) through nasal delivery systems; (3) nasal cannula if air flow of ≤2 L per minute; or (4) no respiratory support (none). Feeding support categories included full enteral feeds, partial enteral feeds, or no enteral feeds. Events of prematurity included episodes of apnea, bradycardia, or hypoxia as reported in nursing documentation and consolidated as 1 event per time regardless of number of signs. During the 12 hours after a ROP study visit, we also collected each infant's respiratory support, nutrition support, and number of events of prematurity.

Predefined criteria for reporting AEs and noteworthy clinical or ocular findings are described in **Table I** (available at www.jpeds.com). AE reporting was required if procedures were terminated due to infant's clinical change, if infant required significant interventions during procedure, or if ocular findings were directly attributed to a procedure. If multiple, related AE terms (for example apnea and bradycardia) were submitted to describe a single event during a ROP procedure, then those terms were consolidated to 1 AE. We consolidated the AE terms apnea, bradycardia, and/or hypoxia into 1 AE category because in premature infants these clinical signs often occur in combination, the initiating event is usually not clear, and there are inconsistencies in how many clinical terms are used to describe these events. Coordinators reviewed the medical charts for important clinical findings, described as AE triggers that may have occurred during the 12 hours after ROP study visit (**Table I**). SAE reporting was required for any event associated with infant death, new surgical indication, or serious event prolonging infant hospitalization. AEs were reviewed by the e-ROP medical monitor and reported to the Data Monitoring and Oversight Committee.

Noteworthy clinical and ocular findings (**Table I**) were reported because they can serve as markers of infant pain