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Safety of ROP Examination and imaging in Premature Infants

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Abstract

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 pre-defined AEs and noteworthy findings reported in a prospective observational cohort study of infants <1251 g birth weight (BW) 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—1,257 infants, mean BW 802 g, had 4,263 BIO and 4,048 imaging sessions (total 8,311 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% versus 12%, p=0.04) even after adjustment for weight and PMA. Noteworthy clinical findings were reported during 8% BIO and 15% imaging exams. Respiratory and nutrition support were not significantly different before and after ROP evaluations.

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

The authors declare no conflicts of interest.

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Conclusions—Retinal imaging by non-physicians 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.

Trial registration—Clinicaltrials.gov: NCT01264276

MeSH Key Words

retinopathy of prematurity; very low birth weight infant; adverse event

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) <1500g 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 post-menstrual 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 exam.(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 non-specific pain or stress.(2, 4–8) Serious adverse events (SAEs) including necrotizing enterocolitis and cardiopulmonary arrest have been reported.(9–11)

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 non-physicians 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 2011–2013, the e-ROP study enrolled 1284 infants with birth weight (BW) < 1251 grams (g) of whom 1257 infants had ROP evaluations at one of twelve United States or a Canadian newborn 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 non-physician 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 to 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 adverse events (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 through nasal delivery systems (CPAP); (3) nasal cannula (NC) if air flow of ≤2 liters 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 one event per time regardless of number of signs. During the 12 hours after a ROP study visits, 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 one AE. We consolidated the AE terms apnea, bradycardia, and/or hypoxia into one 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 and stress or complications related to procedure. Clinical findings were often transient and resolved with a pause in the procedure. Slightly different descriptions of ocular findings (Table I) were used for BIO and imaging because imagers were not trained to describe ocular findings in the same terms as ophthalmologists.(13)

Statistical Analyses

We performed descriptive analysis (means, medians, standard deviations, proportions) for birth characteristics and infant characteristics at time of an ROP study visit. We compared infant characteristics (BW, GA, sex, race/ethnicity, inborn/outborn) between infants with any AEs and those without any AEs during the study period using two-sample t-test for means, and Chi-squared tests for proportions.

We compared infant characteristics (weight, PMA, enteral nutrition status, respiratory support status) at the time of ROP study visits with AEs and at visits without AEs using two-sample t-test for means, and Chi-squared tests for proportions. We further performed these comparisons using multivariate logistic regression to adjust the weight and PMA at the ROP study visits.

To determine whether infant's clinical status changed after ROP study visits, we used McNemar test to compare categories of infant's enteral nutrition support (full, partial, none), respiratory support (ventilator, CPAP, NC, or none), and events of prematurity, apnea, bradycardia, or hypoxia, (0–1 events, 2–5 events, and >5 events) during the 12 hours before and after ROP study visits. We also compared the mean number of events of prematurity 12 hours before and after ROP study visits using paired t-test. All the statistical comparison were made in SAS (SAS Institute Inc., Cary, NC) and two-sided p-value <0.05 was considered as statistical significance.

Results

AEs and noteworthy clinical and ocular findings (Table I) were evaluated for the 1257 e-ROP infants who had a mean BW of 864 g and GA 27 weeks, enrolled between 2011–2013. Infants had 4263 ROP study visits that included 4263 BIO exams by ophthalmologists and 4048 imaging sessions by non-physicians on the same day, for a total of 8311 ROP procedures. The median time separating BIO and imaging was 24 minutes, interquartile range: 10 to 57. Imaging occurred after BIO in 66% of study visits. Imaging was not attempted in 5% of ROP study visits (205 imaging sessions) due to PMA less than 32 weeks (44 imaging sessions, 1%), pre-existing clinical illness (85, 2%), off unit (10, 0.2%), parent refusal (56, 1.3%) or other (95, 2%).

Infants had a median of 3 ROP study visits beginning at a median (range) PMA of 33 (30–42) weeks and ending at median (range) PMA of 38 (32–47) weeks. The later PMA at enrollment occurred when an outborn infant was transferred into an e-ROP clinical center for ROP treatment, surgery, or management of worsening clinical morbidities including severe infections, necrotizing enterocolitis, and chronic lung disease. ROP treatment occurred in 14% of infants(14).

Description of Adverse Events during or shortly thereafter ROP study visits

There were no SAEs related to ROP study visits. During ROP study visits, no infants required intubation or cardiac compressions. Sixty-five AEs were reported among 61 infants for an AE rate of 4.9% infants (61/1257), 1.5% ROP study visits (65/4263), or 0.8% total ROP procedures (65/8311 BIO + imaging) (Table II).

There were 59 AEs (90%) that occurred during ROP study visits that were primarily due to apnea, bradycardia, and/or hypoxia (68%), tachycardia (16%), or emesis (8%) (Table II). These symptoms resolved by the end of ROP procedures. One infant developed a retinal hemorrhage directly attributed to imaging.

There were 6 AEs (10%) that occurred shortly after ROP study visits, within 12 hours (Table II). These AEs were identified using the pre-defined AE triggers (Table I) and included 3 infants who were intubated, 2 who required increased respiratory support, 1 who stopped enteral feeds and received antibiotics. None of these 6 AE’s occurred within an hour of ROP study visit procedures and all were unrelated to ROP study visit procedures.

Infant characteristics associated with AEs

Nearly a third of infants were born weighing less than 750 g or extremely premature with GA 22–25 weeks. This cohort is further characterized by AE status in Table III. Infants with AEs were born at younger GA compared with infants without AEs (Table III).

At the time of a ROP study visit and when averaged across all ROP study visits, infants weighed 2055 g (range 620–4570) and were 36 weeks PMA (range 30–47) (Table IV). Most infants (76%) were receiving full enteral nutrition, and 8% of infants were receiving none. Most infants were receiving respiratory support; 12% mechanical ventilation, 23% nasal CPAP, 33% nasal cannula (≤2 L/min). In the 12 hours before an ROP study visit, 36% of

infants experienced at least 1 event of prematurity, specifically apnea, bradycardia, and/or hypoxia, and 6% of infants had more than 5 events (range 6–42).

At the time of an ROP visit with an AE compared with an ROP visit without an AE, infants on average were smaller (1855 vs 2058g, $p<0.01$), younger PMA (35.5 vs 36.3 weeks, $p=0.02$), and more likely to be on a ventilator (25% vs 12%, $p=0.03$) (Table IV). Except for one AE that occurred at 31 weeks and 6 days, all AEs occurred between 32–45 weeks PMA. When weight, PMA and ventilator support were considered together in a multivariate logistic regression model for AEs, only ventilator support remained significant ($p=0.04$). BIO occurred first before imaging in 75% of ROP study visits with AEs compared with 65% of visits without AEs; however this difference was not significant ($p=0.10$).

Difficulty in determining if BIO or imaging directly contributed to AEs

For most AEs, it was difficult to determine if they were specifically related to BIO, imaging, medications, positioning, clinical illness, or a combination of factors. One-third of AEs were reported to have been probably or definitely related to BIO (4 AEs) or imaging (18 AEs). The remaining 37 AEs were reported to have been possibly, unlikely, or unrelated to either or both procedures. Imaging was terminated in 35 imaging sessions (35/4048, 0.8%) for clinical events that included apnea, bradycardia, and/or hypoxia (29), tachycardia (4), or emesis (2); however only 11 of these terminated sessions were reported to have been probably or definitely related to imaging. In 76% of these terminated imaging sessions, BIO had already been completed.

Study coordinators entered comments for 54% (35/65) of the AEs that described associated findings, interventions provided, or other factors that may have contributed to the AE. Some comments provided insight into specific etiology such as hypoxia with supine positioning, heart rate changes associated with positioning for imaging, and emesis during imaging. Often the infant was reported to have clinical changes such as tachycardia, hypoxia, or emesis prior to start of a ROP procedure that then persisted or worsened during the procedure. Comments also reported nurse or parent requests for termination of imaging due to an infant's clinical illness or on-going clinical events during an imaging evaluation, a study procedure that was not necessary for clinical care.

Noteworthy clinical findings reported during eye examination and imaging

Noteworthy clinical non-ocular findings, as defined in Table I, were reported in 8.3% BIO exams and 14.8% imaging sessions. Hypoxia (5.3% BIO, 7.3% imaging), bradycardia (2.8% BIO, 5.9% imaging), and tachycardia (1.2% BIO, 3.8% imaging) were the most frequent clinical findings. Apnea, tachypnea and emesis were each reported in less than 1% of ROP study visits by either BIO or imaging.

Noteworthy ocular findings during eye examination and imaging

Noteworthy ocular findings, as defined in Table I, were reported in 8% BIO and 9% imaging sessions. Retinal hemorrhage and "other" were the most common noteworthy ocular finding on both eye exam and imaging. One ocular AE for a retinal hemorrhage attributed to imaging was reported. Comments associated with "other" category primarily included

descriptions of haziness, hemorrhages in the retina, sclera, conjunctiva or vitreous, or other descriptive characteristics of ROP. There were no reported cases of hyphema or closure of the central retinal artery for >30 seconds during ROP evaluations.

Key safety measures before and after ROP evaluation

In the 12 hours before and after an ROP evaluation, information regarding nutrition and respiratory support was available for 4219 (99%) of the 4263 ROP study visits and information regarding events of prematurity was available for 3957 (93%) of ROP study visits. In the 12 hours after ROP study visits compared with 12 hours before ROP study visit, most infants continued to receive the same categories of nutrition support (94%), respiratory support (96%), and apnea event frequencies (88%) (Table V). Among the infants with clinical change in respiratory or nutrition support after ROP procedures, there was no significant difference in the proportion of infants who were clinically worse and those who were clinically better ($p>0.05$, Table V). After ROP study visits 6.9% of infants had more apnea, bradycardia, or hypoxia events whereas 5.5% had less events ($p=0.01$). There was no difference in the average number of events (mean 1.3 events, sd 3) over the 12-hour time frame both before and after ROP study visits ($p=0.61$). The number of events for the 12 hours after an ROP visit often included events that occurred during the ROP procedures.

DISCUSSION

The e-ROP study provides a unique and detailed safety assessment of ROP screening procedures using a specific monitoring plan with predefined criteria for SAEs, AEs, and noteworthy findings in a large observational cohort study. ROP evaluations by either BIO or imaging appeared safe based on no SAEs associated with ROP procedures and low frequency of AEs during ROP evaluation procedures. There was no significant difference in respiratory or nutrition support, before or after ROP procedures.

Noteworthy clinical findings such as bradycardia, tachycardia, and hypoxia were more common than AEs and were consistent with smaller studies.(12, 15–17) Clinical findings that occur during ROP screening procedures highlight the fragility of extremely premature infants, their propensity to have apnea, bradycardia and hypoxia events, as well as the pain response and oculocardiac reflex invoked by ROP evaluation procedures.

The AE frequencies and noteworthy clinical events found in this study may be higher than what would occur if only a single ROP evaluation procedure, BIO or imaging, was used. In addition, this cohort of infants was likely to be sicker than the average infant undergoing ROP screening because only infants with birth weights of <1251g were eligible and there was a high proportion of outborn infants who were transferred into e-ROP clinical centers for higher levels of care, infants born at 22–25 weeks GA, and infants who required mechanical ventilation beyond 34 weeks PMA.

Regardless of risk, sick premature infants need to have ROP screening performed to identify ROP and to be given timely treatment for type 1 ROP. Specific information regarding what constitutes a significant event or how to prevent events during ROP screening procedures has been limited. Studies that have reported frequencies of systemic complications have

been small and often excluded the sickest infants such as those requiring respiratory support, with neurologic injury, or with infections. Large studies of ROP typically focus on the epidemiology of ROP, ocular outcomes, and SAEs; detailed descriptions of safety monitoring plans, definitions or frequencies of noteworthy clinical events or AE have not generally been provided.(18–20) Large studies evaluating telemedicine programs with retinal imaging typically report no systemic complications or AEs.(18, 20, 21) In one study, imaging procedures were limited to 2 minutes and this may have decreased the frequency of systemic complications; however 20% of imaging sessions were repeated 24–48 hours after initial imaging due to inadequate images.(21)

Noteworthy ocular findings consisted mostly of retinal, scleral, or conjunctival hemorrhages or haziness. Retinal hemorrhages can occur in premature infants, especially those with ROP. Imaging can cause a retinal hemorrhage in premature infants, as was detected in one infant in this study. Relating hemorrhage to imaging relies on detecting the hemorrhage while imaging or seeing a new hemorrhage on BIO if the BIO exam was performed shortly after imaging. Studies that performed BIO after imaging, such as in the PHOTO-ROP study(18), have not reported data regarding retinal hemorrhages, but would be more ideally suited to determine how often retinal hemorrhages occur during or shortly after imaging in premature infants.

In many cases it was difficult to determine if AEs or noteworthy clinical findings were associated with BIO, imaging, the combined impact of both procedures, infant positioning for procedures, mydriatic medications, or underlying clinical illness. Data recorded was designed to assess patient safety and not specifically to determine which of the two study procedures led to AEs or clinical findings. Clinical centers attempted to alternate which study procedure was performed first, but clinical care of the infant always superseded the order of study procedures and BIO often was performed first. We did not collect the duration of BIO or imaging procedures or the dosing information of eye medications. We did not conduct a time trend analysis or evaluate the impact of imager experience because sites began enrolling at different times and had different imagers over time. Sites did undergo a lead-in phase during which imagers were required to submit images for quality assessment and information about safe conduct of imaging prior to e-ROP enrollment. Of note, the site with the most AEs had the most experience in imaging as standard of care prior to this study.

The higher frequency of AEs and clinical findings during imaging draws attention to the risks associated with both imaging and BIO for ROP screening. Specific aspects of imaging procedures seemed to be associated with clinical findings including supine positioning, placing the speculum beneath the lids, positioning the camera for retinal images, and attempting to visualize the nasal retina. The imaging protocol required six specific images for each eye and infants may have fatigued if the imaging procedure was prolonged. BIO may be associated with fewer events if the procedure was performed without a speculum, allowed infant to be in a somewhat side-lying position, or if they were able to quickly exclude the presence of type 1 or 2 ROP they may have limited the extent of their exam.

Additionally, the e-ROP study design had an inherent reporting bias during imaging compared with BIO. We suspect that the threshold for clinical findings that led to imaging termination and AE reporting was lower during imaging because only BIO was used for clinical care. Additionally, study coordinators who often assisted imagers during imaging sessions may have been more likely to report AE and clinical findings compared with ophthalmologists who typically performed their exam without a study coordinator.

Regardless of the specific ROP procedure used, infants are at risk for AEs and clinical findings during the procedure. These events occurred despite significant efforts to maximize infant comfort and safety during ROP screening procedures and must be put in context of detecting a potentially blinding disorder. Study personnel training emphasized the following guidance: (1) partner with bedside nursing; (2) attend to thermoregulation, support equipment, and infant positioning; (3) optimize pain management; (4) adhere to infection control practices; and (5) pause study procedures for cardiac and respiratory changes during ROP procedures.

It is important to establish clear definitions, safety monitoring plans, and transparent reporting systems for AE and noteworthy clinical findings during ROP procedures so that we can to better understand the relationships between infant characteristics, ROP procedures, and clinical events and to determine how to minimize clinical events. A standardized approach would allow comparison of event frequencies across studies, among different telemedicine programs, or between different NICUs. Decreasing the frequency of events during ROP imaging will likely lead to improved imaging quality, decreased need for repeated imaging, and better acceptance of imaging procedures by parents and NICU staff. Quality improvement and risk reduction projects may be helpful in efforts to reduce the frequency of AEs or clinical findings during ROP screening.

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List of abbreviations

AE	adverse event
BW	birth weight
BIO	binocular indirect ophthalmoscopy
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

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Appendix 1

Members of the e-ROP Study Cooperative Group include (PI; principal investigator):

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Table 1

Pre-specified definitions for adverse event triggers and noteworthy clinical or ocular findings. Adverse event triggers refer to those clinical changes that would lead to consideration of adverse event reporting.

Adverse event triggers	**Definition**
Termination of BIO / imaging session	Any event that requires the ophthalmologist or imager to stop ROP their evaluation and cancel any further exam or imaging due to clinical instability of infant
Event requiring intubation	Bradycardia or hypoxia event requiring intubation or re-intubation
Event requiring cardiopulmonary resuscitation (CPR)	Event requiring positive pressure ventilation and chest compressions with or without epinephrine
Initiation of inotropic medications	Initiation of dopamine, dobutamine, epinephrine, milrinone
Evaluation for serious infections	Initiation of intravenous antibiotics and obtaining a blood culture
Evaluation for necrotizing enterocolitis (NEC)	Stopping enteral nutrition, obtaining an abdominal Xray and blood culture, and initiation of intravenous antibiotics
Significant change in respiratory support	Event requiring increase in respiratory support modality, such as a change from nasal cannula to CPAP or CPAP to ventilator
Other	Event felt to be clinically significant, requiring treatment to stabilize infant
Noteworthy clinical findings	
Apnea	Respiratory pause of at least 10 second
Bradycardia	Heart rate < 80 beats per minute sustained for > 30 seconds
Tachycardia	Heart rate > 200 beats per minute sustained for > 30 seconds
Tachypnea	Respiratory rate more than 70 breaths per minute sustained for > 30 seconds
Hypoxia	Oxygen desaturation to < 80% for > 30 seconds or increased inspired oxygen > 20% sustained for > 60 seconds
Emesis	Vomiting
Other	Event felt to be clinically significant and specified in free text
Noteworthy ocular findings, report AE if finding was attributed to ophthalmoscopy or imaging	
Binocular indirect ophthalmoscopy	Hyphema, retinal hemorrhage, vitreous hemorrhage, closure of retinal artery for > 30 seconds
Digital imaging session	Blood in front of iris, blood on retina or in region of retina, obscured view of retina

Table 2

Description of AEs during or shortly after ROP study visits (n=65 AEs)

AEs during ROP evaluation (n=59)	***n events (%)***	
Apnea, bradycardia, and/or hypoxia	*42*	*(71%)*
Tachycardia	*9*	*(15%)*
Emesis	*5*	*(8%)*
Epistaxis	*1*	*(2%)*
Arrhythmia (bradycardia)	*1*	*(2%)*
Retinal Hemorrhage	*1*	*(2%)*
AEs after ROP evaluations (n=6)	***n events (%) and associated clinical circumstances***	
Apnea, bradycardia, & hypoxia events	4	(67%)
Required bag mask positive pressure ventilation & increased respiratory support		1 due to water droplets from CPAP device, resolved 2 due to opiates & ROP laser surgery, resolved with intubation 1 due to GBS sepsis, resolved with intubation and antibiotics
Feeding intolerance	1	(17%)
Required IV fluids and antibiotics		Infant with emesis & abdominal distention. Stopped feeds, started antibiotics, symptoms resolved. Resumed full enteral feeds within 24 hours. No evidence NEC.
Respiratory insufficiency	1	(17%)
Required increased mode of respiratory support		Increased respiratory distress that resolved with change in respiratory support from nasal cannula to CPAP due to chronic lung disease and recent weaning off CPAP.

Table 3

Comparison of birth characteristics between infants with and those without AE

Birth Characteristics		e-ROP cohort infants			p value*
		Total (n=1257)	**without AEs (n=1196)**	**with AEs (n=61)**	
GA mean weeks (SD) [range]		27.0 (2.2) [22.7–35.1]	27.0 (2.2) [22.7–35.1]	26.4 (1.8) [23.7–32.1]	**0.03**
22 −25 weeks n (%)		436 (35)	404 (34)	32 (52)	**0.02**
26 or 27 weeks n (%)		420 (33)	406 (34)	14 (23)	
28 or 29 weeks n (%)		265 (21)	253 (21)	12 (20)	
≥ 30 weeks n (%)		136 (11)	133 (11)	3 (5)	
BW mean grams, (SD) [range]		864 (212) [330–1250]	866 (214) [330–1250]	824 (183) [476–1180]	0.13
<500 grams	n (%)	34 (3)	32 (3)	2 (3)	0.18
500–749 grams	n (%)	386 (31)	367 (31)	19 (31)	
750–999 grams	n (%)	444 (35)	416 (35)	28 (46)	
1000–1250 grams	n (%)	393 (31)	381 (32)	12 (20)	
Male Gender n %		638 (51)	601 (50)	37 (61)	0.11
Inborn at e-ROP center n (%)		792 (63)	752 (63)	40 (66)	0.67
Race/Ethnicity					0.42
Non-Hispanic white		621 (49)	588 (49)	33 (54)	
Non-Hispanic black		366 (29)	346 (29)	20 (33)	
Hispanic		122 (10)	119 (10)	3 (5)	
Other/Unknown		148 (12)	143 (12)	5 (8)	

*p value for difference between infants with and without AEs using two-sample t-test for mean and Chi-squared test for proportional difference.

Abbreviations: GA, gestational age; BW, birth weight

Table 4

Comparison of infant characteristics at time of ROP study visits

Infant Characteristics	ROP study visits			
	All visits (n=4238)	**Without AE (n=4173 visits)**	**With AE (n=65 visits)**	**p value* **(adjusted)**
Weight (grams) mean (SD)	2055 (585)	2058 (585)	1855 (557)	0.006 (0.17)
PMA (weeks) mean (SD)	36.3 (2.6)	36.3 (2.6)	35.5 (2.6)	0.02 (0.57)
PNA (weeks) mean (SD)	9.8 (3.3)	9.8 (3.3)	9.2 (3.2)	0.12
BIO exam occurred 1st and imaging occurred 2nd or was deferred n (%)	2738 (66)	2690 (66)	48 (75)	0.10
Enteral nutritional status n (%)				**0.15§**
NPO	322 (8)	313 (7.5)	9 (14)	
Partial enteral feeds	675 (16)	666 (16)	9 (14)	
Full enteral feeds	3241 (76)	3194 (77)	47 (72)	
Respiratory support status n (%)				**0.03^ (0.04)**
Ventilator	508 (12)	492 (12)	16 (25)	
CPAP	975 (23)	955 (23)	20 (31)	
Nasal Cannula ≤2L/min	1398 (33)	1383 (33)	15 (23)	
No Support	1328 (32)	1314 (32)	14 (22)	

§ NPO versus all other forms of nutrition support

^ ventilator versus all other forms of respiratory support

* p value for difference between infants with and without AEs using two-sample t-test for mean and Chi-squared test for proportional difference

** p value for multivariable logistic regression with weight, PMA, and ventilator support at ROP visit

Abbreviations: PMA, postmenstrual age; PNA, postnatal age; BIO binocular indirect ophthalmoscopy; NPO nils per os; CPAP all forms of nasal, continuous positive airway pressure; NC nasal cannula.

Percentages may not add up to 100% due to rounding.

Table 5

Clinical status of infants during the 12 hours after ROP study visits compared to the 12 hours before ROP visit.

Categories of support or events Listed in order of most support/events to least support/events	Status after ROP evaluation compared to before			
	Same **No change in support or event category**	**Clinically Worse** **more support or more events**	**Clinically Better** **less support or less events**	**p value***
Enteral nutrition support (none, partial, full)	4069 (94.4%)	67 (1.6%)	83 (2.0%)	0.19
Respiratory support (ventilator, CPAP, NC, none)	4031 (95.5%)	81 (1.9%)	107 (2.5%)	0.06
# apnea, bradycardia, hypoxia EVENTS over 12 hours (>5, 2–5, 0–1 events)	3463 (87.5%)	275 (6.9%)	331 (5.5%)	0.01

* p value from McNemar's test

Abbreviations: CPAP continuous nasal positive airway pressure, NC nasal cannula, EVENTS consolidated events including apnea, bradycardia, and/or hypoxia as noted on nursing daily summary