Purpose: To assess proangiogenic factors and inflammatory mediators in the tears of preterm infants and correlate them with retinopathy of prematurity (ROP).

Methods: Twenty Asian Indian infants were subjected to tear sample collection during the course of their ROP screening. Infants born ≤ 2000 grams and/or ≤ 34 weeks were enrolled. The first sample was collected before a postnatal age of thirty days and subsequent tear samples during follow-up visits until either of the three outcomes were achieved: mature retina without ROP, spontaneously regressed ROP or treatment required ROP. Tear samples were collected using Schirmer strips (15 mm) for each eye at each visit. Two gestational age matched cohorts: Group 1: any stage ROP (n=10 cases) and Group 2: No ROP (n=10 controls) were correlated for the clinical outcomes and tear concentrations of proangiogenic factors (VEGF-A, angiogenin and fractalkine), adhesion molecules (VCAM-1 and ICAM-1) and inflammatory mediators (IL-6, IL-8, RANTES, CD62L and MCP-1) which were assessed using cytometric bead array. Statistical analysis was done using graphpad prism 6.

Results: The level of VEGF-A was significantly upregulated (CI -632.7 to -187.3, p=0.004) and angiogenin (p=0.02) were significantly increased between the first and final visit in infants with ROP. At final presentation, infants with ROP had a significantly higher level of fractalkine (CI -632.7 to -187.3, p=0.04) in infants with ROP compared to the No ROP group in the final visit sample. The level of VEGF-A (p<0.0001) and angiogenin (p=0.02) were significantly increased between the first and final visits in ROP samples during follow-up visits until either of the three outcomes were achieved: mature retina without ROP, spontaneously regressed ROP or treatment required ROP. Tear samples were collected using Schirmer strips (15 mm) for each eye at each visit. Two gestational age matched cohorts: Group 1: any stage ROP (n=10 cases) and Group 2: No ROP (n=10 controls) were correlated for the clinical outcomes and tear concentrations of proangiogenic factors (VEGF-A, angiogenin and fractalkine), adhesion molecules (VCAM-1 and ICAM-1) and inflammatory mediators (IL-6, IL-8, RANTES, CD62L and MCP-1) which were assessed using cytometric bead array. Statistical analysis was done using graphpad prism 6.

Conclusions: This pilot study demonstrates that tears of preterm infants contain angiogenic and inflammatory factors that may be assessed non-invasively. VEGF-A, angiogenin, fractalkine and RANTES were significantly upregulated in infants with ROP at different PMAs. This may help us better understand ROP progression and response to therapy.
first phase of ROP and lower DHA week 32 corresponding to the beginning of the second, proliferative phase of ROP were associated with an increased risk of severe ROP. Since high levels of LA and ALA affect their conversion to LC-PUFA, studies on how to optimize lipid supply to very preterm infants are needed.

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Support: Swedish Research Council

Clinical Trial: NCT02760472

Program Number: 4736
Presentation Time: 4:15 PM–4:30 PM
Early detection of potentially severe ROP on remote image grading


Purpose: Among the 447 eyes with referral-warranted (RW) ROP (stage 3 ROP, zone I ROP, plus disease) on diagnostic exam in the “Telemedicine approaches to evaluating acute-phase ROP (e-ROP)” study, image grading detected RW-ROP earlier than diagnostic exam in 191 (43%) eyes by about 15 days. We describe the characteristics of these eyes to provide insights into what types of ROP are most easily detected early by image assessment.

Methods: e-ROP images were graded remotely by trained non-physician readers using a standard protocol. We undertook a descriptive analysis of zone and stage of ROP and presence of plus disease in 191 eyes in which RW-ROP was noted on imaging before it was documented on clinical examination (Early) and compared them to 200 eyes with RW-ROP noted at the same time by imaging and clinical examination (Same). Demographic characteristics of these two groups of infants, including birth weight (BW), gestational age (GA), and postmenstrual age (PMA) at RW-ROP imaging session are compared.

Results: BW and GA were similar for infants with Early or Same RW-ROP eyes (p=0.10). 60% of 191 Early eyes were noted to have RW-ROP findings on image grading by 34 weeks PMA, compared to 38% of 200 Same eyes (p=0.001). More than half of Early eyes showed positive RW-ROP clinical findings within 2 weeks. When comparing image grading with RW-ROP first found in exam results, Stage 3 ROP was noted in image evaluation in 79% (151/191) Early eyes and in 86% (172/200) Same eyes (p=0.08) and for the presence of zone I ROP in 30% (57/191) Early vs 32% (64/200) Same (p=0.64). For posterior pole vessels, 16% (30/191) of Early eyes and 23% (45/200) of Same eyes (p=0.09) were graded as plus disease on clinical exam. Majority of early eyes (>75%) was consistently called RW-ROP positive by imaging evaluation and agreed with exam finding in 87% of eyes when eye exam subsequently found RW-ROP.

Conclusions: In a majority of both Early and Same eyes, stage 3 was the factor that determined the designation for RW-ROP while zone 1 ROP accounted for a significant proportion and plus disease played a relatively minor factor in the RW-ROP determination. In the majority of Early RW-ROP eyes, the image findings were consistent and RW-ROP was later noted on the examination. As use ofROP telemedicine is used more widely, development of standard approaches and protocols are essential.

Commercial Relationships: Graham E. Quinn, None; Gui-Shuang Ying, None; Agnieszka Baumritter, None; Wei Pan, None; Ebenezer Daniel, None

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Clinical Trial: NCT01264276

Program Number: 4737
Presentation Time: 4:30 PM–4:45 PM
Is there clinical utility for a continuous severity score for plus disease in ROP?

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Purpose: The International Classification for ROP (ICROP) has defined ROP in terms of zone, stage, and plus disease. However, each of these have been shown to demonstrate high levels of inter-observer variability. We recently published data showing that inter-expert discrepancies in plus disease diagnosis (plus vs. pre-plus vs. normal) are due to differences in cut-points for disease severity along a continuous spectrum of vascular abnormality. The purpose of this study is to propose a more continuous 9-point ROP severity scale, and to evaluate its clinical utility as a screening and diagnostic tool.

Methods: 281 infants were identified as part of a multi-center, prospective, ROP cohort study. A 9 level ROP plus disease severity score was determined for each image by averaging the image-based disease classifications (plus vs. pre-plus vs. normal) by 3 graders masked to the clinical ophthalmoscopic diagnosis. Levels 1-3 (all with unanimously “normal” vessels) were subdivided based on the stage classification. We analyzed the relationship between the ROP severity score and ICROP classifications, including referral-warranted ROP (RWROP, defined as zone I or stage 3 or plus disease) and treatment-requiring ROP (defined as type 1 ROP). Area under the receiver operating characteristic curve (AUC) scores were calculated for the ROP severity score as a screening tool for type 1 ROP.

Results: 1553 study eye examinations from 281 infants were included in the study. 249 examinations were classified as RWROP, and 79 as type 1 ROP. The Table displays the percentage in each severity scale with zone I, stage 3, plus disease, or RWROP.

<table>
<thead>
<tr>
<th>Severity Score</th>
<th>Zone I</th>
<th>Stage 3</th>
<th>Plus Disease</th>
<th>RWROP</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>86%</td>
<td>32%</td>
<td>23%</td>
<td>60%</td>
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<td>Type 2</td>
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</table>

Conclusions: This 9 point ROP severity score is associated with clinically significant ROP and demonstrates promise as a screening and diagnostic tool for ROP. In this analysis, the severity score was determined by averaging multiple plus disease classifications. We have shown that similar relative scores may be obtained using pairwise comparisons (assigning a numerical score based on relative comparison to standard images) and using computer-based image analysis (CBIA). In the future, these quantitative methods have potential to improve the objectivity of plus disease diagnosis, improve monitoring of disease progression, and provided added value to telemedicine screening programs.
One hundred and seven infants (n=189 eyes) were examined between 8-15 months CA. Mean refractive error was -3.2±4.38 diopters (range -18.50 to +6.50, n=179/189 eyes). Mean VA was 0.9±3.5 logMAR (range 0.00 to 2.00; n=125/189 eyes). Eighty-six infants (n=151 eyes) were examined at 3 years. Mean refractive error was -5.2±7.89 diopters (range -21.00 to +2.25, n=141/151 eyes). Mean VA was 0.41±0.38 logMAR (range 0.00 to 1.90, n=113/151 eyes).

**Conclusions:** We report lower rates of unfavorable structural outcomes following laser photocoagulation for type 1 ROP in the decade after ETROP. Our results highlight the value of reporting upon institutional treatment-related outcomes when obtaining informed consent for ROP management. This is particularly important when parents are offered the choice between laser and anti-vascular endothelial growth factor injection as treatment modalities.

**Commercial Relationships:** Seema Emami, None; Maram Isaac, None; Kamiar Mireskandari, None; Nasrin N. Tehrani, None

**Program Number:** 4739

**Presentation Time:** 5:00 PM–5:15 PM

**Diagnostic Accuracy of Ophthalmoscopy vs. Teledmedicine in Retinopathy of Prematurity Examination**

**Purpose:** Retinopathy of prematurity (ROP) examinations have traditionally been performed using binocular indirect ophthalmoscopy (BIO). Teledmedicine using digital fundus imaging (DFI) is an emerging strategy that may improve the delivery of ophthalmic care. Traditional teledmedicine studies have assessed accuracy of teledmedicine compared to BIO as a gold standard. However, there is little published literature that directly compares the accuracy of DFI vs. BIO using a consensus reference standard.

**Methods:** We developed a web-based platform to allow storage and interpretation of wide-angle fundus photos of infants undergoing ROP examinations. As part of a prospective cohort study, infants who met screening criteria at 7 participating centers were examined directly via BIO by experienced clinicians and indirectly via DFI grading by 3 trained graders independently. These examination findings were combined into a consensus reference standard diagnosis for each imaging session for zone, stage, plus and category. We calculated the agreement of both DFI and BIO with the gold standard using percent agreement and weighted kappa statistics.

**Results:** A total of 1553 eye examinations were classified using both DFI and BIO. On average, BIO was slightly more accurate than DFI in identifying zone (91% vs 89%, p<0.01), stage (88% vs 75%, p<0.01), and overall disease category (84% vs 77%, p<0.01), whereas DFI was slightly more accurate than BIO in diagnosing plus disease (92% vs 88%, p<0.01). There was significant inter-grader variability in both groups (Table 1). BIO was more sensitive in identifying stage 3 disease (85% vs 73%, p<0.01; n=136), but not zone I (78% vs 78%; n=165), plus disease (74% vs 79%, p=0.41; n=50), or any referral-warranted ROP (RWROP, defined as Stage 3, Zone I, or Plus disease; 84% vs 79%, p=0.10; n=251).

**Conclusions:** This study compared the accuracy and sensitivity of DFI to BIO in ROP examination. Key findings were: 1) Accuracy of ROP diagnosis varies between graders, both using DFI and BIO; 2) There was no significant difference in the sensitivity of BIO and DFI to detect RWROP; 3) BIO was slightly more accurate in identifying zone, stage, and category of ROP, while DFI was slightly more accurate in identifying plus disease. These results show that neither...
Retinal microanatomy development on spectral domain optical coherence tomography and visual acuity in preterm infants

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Purpose: Retinopathy of prematurity (ROP), even in milder forms, often correlates with vision loss (Arch Ophthalmol. 2010; 128(6):663-71). We investigated preterm retinal development by handheld, bedside spectral domain optical coherence tomography (SDOCT) imaging and correlated with preterm birth, ROP, and visual acuity (VA).

Methods: Under a Duke IRB protocol, we enrolled and longitudinally imaged preterm infants undergoing ROP examination between 30 weeks (wks) post menstrual age (PMA) and 9 months (mos) corrected age, using a portable SDOCT system (Bioptigen, RTP, NC). We divided infants into 6 age groups: 30-32, 33-36, 37-42, 43-45, 51-53, and 75+ wks (approximately 9 mos) PMA. By age group, we analyzed for cystoid macular edema (CME), central foveal thickness (CFT), foveal-parafoveal (F-P) ratio, averaged ellipsoid zone (EZ) distance from the fovea, EZ presence and height at the fovea, and subfoveal choroidal thickness (SFCT). We evaluated VA with Teller acuity cards at 9 mos. Per normative data, normal VA was defined as ≥3.70 cycles per degree (Trans Am Ophthalmol Soc. 2014; 102: 235).

Results: 50 infants (mean gestational age (GA) 25.5 ± 2.1 wks, birthweight 801.6 ± 276.0 g) were enrolled and VA tested in 21 infants in this early analysis. CME first presented at 30-32 wks in 33% eyes, was most common at 37-42 wks in 71% of eyes, and persisted at 9 mos in 10% of eyes (Fig 1). Infants with CME at 37-42 wks PMA and infants with max ROP stage 3 vs stage 2 had lower VA (p = 0.04, 0.05). Mean VA did not differ significantly with the presence of EZ at the fovea, CME, or ROP treatment and did not correlate with GA, birthweight, CFT, EZ distance, or SFCT. For every 1 micron/4 week increase in EZ height development rate, the odds of normal VA increased by 7.5 (CI 0.94, 61; p = 0.058).

Conclusions: Abnormalities in the preterm retina including CME presence, higher maximum ROP stage, and lowered EZ height may be associated with lower VA at 9 mos. Findings indicate that retinal, particularly photoreceptor, development may correlate with VA outcomes. Further studies are warranted.