American Academy of Ophthalmology
The Eye M.D. Association

Influence of Fluorescein Angiography on the Diagnosis and Management of Retinopathy of Prematurity

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Purpose: To examine the influence of fluorescein angiography (FA) on the diagnosis and management of retinopathy of prematurity (ROP).

Design: Prospective cohort study.

Participants: Nine recognized ROP experts (3 pediatric ophthalmologists and 6 retina specialists) interpreted 32 sets (16 color fundus photographs and 16 color fundus photographs paired with the corresponding FA images) of wide-angle retinal images from infants with ROP.

Methods: All experts independently reviewed the 32 image sets on a secure website and provided a diagnosis and management plan for the case presented, first based on color fundus photographs alone, and then based on color fundus photographs and corresponding FA images.

Main Outcome Measures: Sensitivity and specificity of the ROP diagnosis (zone, stage, plus disease, and category, i.e., no ROP, mild ROP, type 2 ROP, and ROP requiring treatment) were calculated using a consensus reference standard diagnosis, determined from the diagnosis of the color fundus photographs by 3 experienced readers in combination with the clinical diagnosis based on ophthalmoscopic examination. The κ statistic was used to analyze the average intergrader agreement among experts for the diagnosis of zone, stage, plus disease, and category.

Results: Addition of FA to color fundus photography resulted in a significant improvement in sensitivity for diagnosis of stage 3 or worse disease (39.8% vs. 74.1%; $P = 0.008$), type 2 or worse ROP (69.4% vs. 86.8%; $P = 0.013$), and pre-plus or worse disease (50.5 vs. 62.6%; $P = 0.031$). There was a nonsignificant trend toward improved sensitivity for diagnosis of ROP requiring treatment (22.2% vs. 40.3%; $P = 0.063$). Using the κ statistic, addition of FA to color fundus photography significantly improved intergrader agreement for diagnosis of ROP requiring treatment. Addition of FA to color fundus photography did not affect intergrader agreement significantly for the diagnosis of stage, zone, or plus disease.

Conclusions: Compared with color fundus photography alone, FA may improve the sensitivity of diagnosis of ROP by experts, particularly for stage 3 disease. In addition, intergrader agreement for diagnosis of ROP requiring treatment may improve with FA interpretation. *Ophthalmology 2015;■:1–8 © 2015 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Clinical examination by indirect ophthalmoscopy has long been the standard method for the diagnosis of retinopathy of prematurity (ROP). On the basis of large, well-designed clinical trials, including the Cryotherapy for ROP and Early Treatment for ROP trials,[1,2] a consensus policy statement was established in the United States for the screening and management of ROP.[3] This policy statement recommended that examinations be performed "using binocular indirect ophthalmoscopy."[3] The policy statement also acknowledged a growing role for digital imaging in ROP, but emphasized the need for further studies to parse out the usefulness of these imaging methods in the diagnosis and management of ROP.

Fluorescein angiography (FA) has been shown to be critical for assessing the retinal vasculature in vasoproliferative disorders such as diabetic retinopathy[4] and exudative age-related macular degeneration in adults.[5] Additionally, FA has an important role in the evaluation and management of pediatric vascular disorders, including Coats' disease,[6] choroidal neovascular membranes,[7] sickle cell retinopathy,[8] ocular tumors,[9] and other conditions.[10,11] Fluorescein angiography appears to be safe in children, including neonates with ROP, with no adverse effects reported in several series.[12–15] Cantolino et al,[16] Flynn et al,[17] and O'Grady et al[18] introduced FA as a method to study retrolental fibroplasia in the late 1960s, and other investigators in this era noted the benefit of FA in

http://dx.doi.org/10.1016/j.ophtha.2015.04.023
ISSN 0161-6420/15

evaluating the peripheral retina in the acute stages of ROP as well as for identifying late complications.[19] These early investigators noted the presence of changes seen on FA that were not visible on clinical examination. Flynn et al[17] used a Zeiss fundus camera (Carl Zeiss Meditec Inc, Dublin, CA) to obtain the angiograms, but because of limitations in obtaining fundus images in neonates with this device, there were limited reports of FA in ROP for many subsequent years.

With the introduction of newer digital wide-angle and ultrawide-field imaging systems, including those designed for pediatric use (e.g., RetCam; Clarity Medical Systems, Inc, Pleasanton, CA),[10,11,20] it is now becoming more common to perform bedside fundus imaging[21,22] and FA[12,23] in the pediatric population. Given that bedside FA is now more accessible and may provide useful information regarding developing retinal vasculature, there has been renewed interest in using this diagnostic method in the evaluation of ROP. Moreover, the shortage of trained ROP experts worldwide has prompted an interest in the role of telemedicine for this disease.[24,25] In turn, there has been particular interest in the usefulness of digital imaging for ROP.

The role of FA in the diagnosis of ROP by digital imaging remains unclear. Fluorescein angiography recently was implemented to evaluate retinal vascular morphologic features in eyes receiving intravitreal anti−vascular endothelial growth factor (VEGF) therapy[26−28]; however, current studies of FA in ROP are predominately descriptive, limiting their clinical impact and conclusions.[12,14,15,26,27,29] As such, a gap exists in understanding the usefulness of FA related to the accuracy of diagnosis and management of ROP by pediatric ophthalmologists and retina specialists. The purpose of this study was to evaluate the influence of FA on the diagnosis and management of ROP by ROP experts using wide-angle fundus images.

Methods

This study was approved as a prospective study by the institutional review board at Weill Cornell Medical College. Informed consent was obtained from all study participants before participation, and waiver of consent was obtained for use of de-identified retinal images. This study was conducted in accordance with Health Insurance Portability and Accountability Act guidelines and adhered to the tenets of the Declaration of Helsinki.

Image Acquisition

Wide-angle images of the posterior retina and corresponding FA images were captured bilaterally from 8 infants with ROP (16 eyes) using the RetCam II (Clarity Medical Systems, Inc.). Images were obtained from infants between 33 and 44 weeks postmenstrual age. For acquisition of FA images, 4 of 8 infants (50%) were imaged in the neonatal intensive care unit without intubation or sedation, whereas the remaining 4 of 8 infants (50%) were imaged in the operating room under sedation.

Consensus Reference Standard Diagnosis

For each image set, a consensus reference standard ROP diagnosis was established. This was accomplished by combining the clinical diagnosis as determined by indirect ophthalmoscopy with the image-based diagnosis from multiple experienced readers, as described previously.[30] This consensus reference standard then was used for the current study.

Study Experts

Eligible participants for this study were defined as board-certified practicing pediatric ophthalmologists or retina specialists who routinely evaluate infants for ROP and met at least 1 of the following criteria: was a principal investigator or certified investigator for the Cryotherapy for ROP study or Early Treatment for ROP study or published at least 2 peer-reviewed articles about ROP. These participants are referred to herein as *experts*.

Study Design

Study experts were directed to a secure website developed by the authors (M.A.K., S.N.P., M.F.C., R.V.P.C.). Initial baseline demographic data were collected from each expert, including what fellowship training had been completed (pediatric ophthalmology, medical retina, surgical retina), years since completion of fellowship, and level of comfort with reading color fundus photographs and FA images in ROP (not comfortable, somewhat comfortable, comfortable). Experts also were asked for the percentage of patients in their clinical practice with type 2 or worse ROP from whom they obtained FA imaging (0%, 1%−25%, 26%−50%, 51%−75%, 75%−99%, 100%), and, finally, whether they believe FA is safe in infants and neonates (yes or no). Type 2 ROP was defined as (1) zone I, stage 1 or 2 without plus disease, or (2) zone II, stage 3 without plus disease. Retinopathy of prematurity requiring treatment was defined as (1) zone I, any stage with plus disease; (2) zone I, stage 3 with or without plus disease; or (3) zone II, stage 2 or 3 with plus disease.

Experts were presented with a series of 8 ROP cases. Each case consisted of baseline demographic information (birth weight, gestational age, and postmenstrual age at the time of imaging) and an image set of color fundus photographs (Fig 1, available at www.aaojournal.org). Color fundus photographs were displayed as a set of 3 retinal images of each eye (temporal, posterior, nasal). For each image set, experts were asked to choose the zone (I, II, II posterior, III); stage (1, 2, 3, 4, 5); plus (no, preplus, plus); category (mild, type 2 ROP, ROP requiring treatment); management (observation, laser only, anti-VEGF only, laser with anti-VEGF, surgery); presence of aggressive posterior ROP (yes or no); and recommended clinical follow-up (less than 1 week, 1 week, 2 weeks, more than 2 weeks). Experts were asked their level of confidence (confident, somewhat confident, not confident) in determining the clinical diagnosis based on color fundus photographs provided and whether they would obtain FA imaging based on the color fundus photographs (yes or no). This was performed in sequential order for each of the 8 cases.

Next, a second image set comprising the same color fundus photographs accompanied by their corresponding FA images was presented for each of the 8 cases in the same sequential order. For each image set, the expert again was asked to determine zone, stage, plus, category, management, presence of aggressive posterior ROP, and recommended clinical follow-up. Experts also were asked to gauge their level of confidence in determining the diagnosis based on color fundus photographs and FA images (confident, somewhat confident, not confident) and whether they believed that the FA images had provided clinically useful information for management purposes (yes or no).

Data Analysis

All data were analyzed using statistical software (Stata/SE version 12.0; StataCorp LP, College Station, TX). A Wilcoxon