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Comparison of Wide-Field Fluorescein Angiography and Nine-Field Montage Angiography in Uveitis

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Abstract

Purpose—To qualitatively and quantitatively compare Optos® fundus camera fluorescein angiographic images of retinal vascular leakage with 9-field montage Topcon® fluorescein angiography (FA) images in patients with uveitis. We hypothesized that Optos images reveal more leakage in uveitis patients.

Design—Retrospective, observational case series.

Methods—Images of all uveitis patients imaged with same-sitting Optos FA and 9-field montage FA during a 9 month period at a single institution (52 eyes of 31 patients) were graded for the total area of retinal vascular leakage. The main outcome measure was area of fluorescein leakage.

Results—The area of apparent FA leakage was greater in Optos images than in 9-field montage images (median 22.5 mm² vs. 4.8 mm², $P < 0.0001$). Twenty-two of 49 (45%) eyes with gradable photos had at least 25% more leakage on the Optos image than on the montage image. Two (4.1%) had at least 25% less leakage on Optos, and 25 (51%) were similar between the two modalities. Two eyes had no apparent retinal vascular leakage on 9-field montage but were found to have apparent leakage on Optos images. Twenty-three of the 49 eyes had posterior pole leakage, and of these 17 (73.9%) showed more posterior pole leakage on the Optos image. A single 200 degree Optos FA image captured a mean 1.50x the area captured by montage photography.

Conclusion—More retinal vascular pathology, both in the periphery and the posterior pole, is seen with Optos FA in uveitis patients when compared with 9-field montage. The clinical implications of Optos FA findings have yet to be determined.

Fluorescein angiography (FA) is an important diagnostic modality in uveitis. In posterior uveitides, FA helps with the assessment of retinal and choroidal lesions, subretinal fluid, retinal perfusion, retinal vascular leakage, choroidal neovascularization (CNV), retinal neovascularization, and cystoid macular edema (CME). In anterior and intermediate uveitides, FA helps with assessment of CME and retinal vascular involvement. Most of

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these pathologies can occur in the retinal periphery in areas not imaged with standard 50 degree FA. Peripheral sweeps and montage photography are commonly used in uveitis patients when the retinal periphery must be imaged. These techniques are labor-intensive, require highly skilled photographers, and do not permit simultaneous imaging of the posterior pole and the periphery.

The Optos® fundus camera (Optos Plc, Dunfermline, Scotland, UK) can capture up to 200 degrees of the ocular fundus in a single photo, greater than the 30 or 50 degree images typically captured by standard fundus cameras.¹ When a single Optos image is compared with seven standard field montage images, the Optos image includes 3.2 times the area of retina imaged in a seven standard field montage.² Comparison of nine field fluorescein images with Optos images in our uveitis clinic has shown that the Optos images capture a larger area. For this reason, we hypothesized that Optos fluorescein images would capture more retinal vascular leakage than the nine field montage.

Furthermore, we hypothesized that Optos fluorescein images reveal more retinal vascular leakage than standard images even in areas that are adequately captured by both cameras. A fundus camera (e.g. Topcon) and a scanning laser ophthalmoscope (SLO, e.g. Optos) have fundamentally different illumination and light capture technologies that result in differing image characteristics. A fundus camera uses the periphery of the objective lens to project the camera's light source onto the fundus.³ The center of the lens then focuses reflected light onto the internal optics of the camera. An SLO on the other hand uses a narrow scanning laser light source that is focused onto the retina by an ellipsoidal mirror.⁴ Because the light source is narrow, a much larger percentage of the pupil is available to capture returning light. The Optos therefore allows for not only wide angle imaging, but also produces a qualitatively different FA image.

At the National Eye Institute (NEI), numerous patients with uveitis-related retinal vascular leakage have had FA performed with a standard fundus camera (nine field montage) and the Optos SLO in the same sitting. Here, we review records from the NEI uveitis service to qualitatively and quantitatively compare these images.

Methods

The records of all uveitis patients who underwent same sitting 9-field montage and ultra-wide field fluorescein angiography using the Optos Optomap Panoramic 200TW between July 1 2011 and April 10 2012 were reviewed retrospectively. Most patients undergoing montage fluorescein angiography also had late Optos imaging during this study period. Patients were identified from the NEI OIS Winstation image database (Ophthalmic Imaging Systems, Sacramento, California). The NEI electronic medical record was reviewed for the following parameters: age, gender, anatomic classification of uveitis, and etiologic diagnosis. Patients were enrolled in one of several prospective National Institutes of Health Combined Neurosciences Institutional Review Board (IRB)-approved clinical research protocols, and charts were reviewed retrospectively under the terms of these protocols and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki.

Informed consent had been obtained from each patient for participation in a clinical research protocol and for each FA. The angiography procedure involved intravenous injection of 5 ml of sodium fluorescein 10% with the patient seated at the Topcon fundus camera (Topcon Medical Systems, Inc., Oakland, New Jersey). Transit images were obtained of the posterior pole with the Topcon camera, and peripheral imaging of both eyes began at approximately two minutes post-infusion. Once requisite peripheral photos for bilateral 9-field montage

were completed, late images of the posterior pole were obtained in both eyes at ten minutes. The patient then moved to the Optos machine for further imaging. Widefield images were obtained with the Optos in both eyes, and color images were also obtained on the Optos machine to assist in clinical correlation. Montage images were made using OIS Winstation software.

Some patients who met inclusion criteria had more than one series of photographs (e.g., multiple clinical visits). In this case, the earliest available visit was included in the study and used for analysis. Multiple late Optos FA images were usually obtained, so one representative image was chosen for analysis. Optos images were chosen based on overall image quality and inclusion of the posterior pole and peripheral pathology. Optos and montage images were processed with I2k alignment software (DualAlign LLC, Clifton Park, New York). Alignment was intended to account in part for differential peripheral distortion between the two modalities. The histogram equalization function in Image J, a Java-based image processing program, was utilized to account for the variability in contrast between the Optos and montage images. This function allows for pixels to be evenly distributed throughout the image intensity range so the resulting image has a flat histogram. Figure 1 is an example of an aligned, adjusted image that was sent for grading.

Two masked, trained graders (DM,DN) independently analyzed the aligned images. Areas of apparent retinal vascular leakage were outlined using the software Image J in both images. Other hyperfluorescent pathologies including staining and window defects were not included in measurements. The outline of the retinal pathology was verified by a third grader (BN). The outlined area was then assessed for surface area and greatest linear dimension (GLD) in pixels for both the Optos image and the montage. These pixel values were then converted into micron values with the assumption of a retinal vein diameter of 125 microns at the margin of the optic disc. The data were then averaged between the two graders to obtain the final values used for analysis. The pairs of photos were assessed for the presence of retinal vascular leakage and categorized as “more,” “less,” or “same.” These categories were defined based on a minimum 1 mm² and 25% difference between the two modalities. Posterior pole leakage was assessed using ten minute late FA images and subjectively categorized as “more,” “same,” or “less” as a secondary exploratory analysis.

To compare the surface area imaged with nine standard field (9SF) montage with the Optos, an artificial eye was used for both Optos and montage imaging. The artificial eye allowed the photographer unlimited time and unlimited eye positioning for ideal image capture. The ratio of the amount of artificial retinal surface area seen in a single Optos image versus the 9SF image was then calculated. A random subset of ten study eyes was then selected for a similar exploratory analysis. The mean ratio of Optos surface area to montage surface area in these ten eyes was calculated.

Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). The Wilcoxon signed rank test was used to compare the area and GLD in the Optos images with measurements from the montage images. It was also used to assess for differences between analyses from aligned and unaligned image pairs.

Results

Same-sitting Optos and 9-field montage FA were performed in 52 eyes of 31 patients with uveitis. In three eyes of two patients, the images were of insufficient clarity to measure FA leakage. These eyes were therefore excluded from the analysis. The mean age of the 30 patients included in the analysis was 38.7 years (range 11–63). Forty eight of the 49 eyes had non-infectious uveitis. Seven patients had intermediate uveitis, 13 had posterior uveitis,

and 10 had panuveitis. There were no cases of anterior uveitis that met the inclusion criteria. Etiologic diagnoses included idiopathic intermediate uveitis (10 eyes), idiopathic posterior uveitis (10), idiopathic panuveitis (9), sarcoid uveitis (6), Vogt-Koyanagi-Harada disease (6), birdshot chorioretinopathy (3), ampiginous chorioretinopathy (2), lupus retinal vasculitis (2), and acute retinal necrosis (1).

The area of apparent FA leakage was greater in Optos images than in 9-field montage images. The median area of leakage in the montage images was 4.8 mm², and the median area of leakage in the Optos images was 22.5 mm² ($P<0.0001$). 22/49 (45%) eyes had at least 25% more leakage on the Optos image than on the montage image. Two of the 49 eyes (4.1%) had at least 25% less leakage on Optos, and 25/49 (51%) were similar between the two modalities including 15 eyes that had no angiographic activity on either modality. Two eyes had no apparent retinal vascular leakage on 9-field montage but were found to have apparent leakage on Optos images. The greatest linear dimension (GLD) of areas of angiographic activity was assessed in addition to area measurements. The median GLD on the montage images was 4.2 mm, while the median on the Optos images was 7.9 mm ($P=0.0006$). 23/49 eyes had posterior pole leakage, and of these 17 (73.9%) showed more posterior pole leakage on the Optos image (Figure 2). In three cases (10%), additional immune suppression was prescribed as a result of Optos FA findings.

On measurement of an artificial eye, a single 200 degree Optos image captured 1.09x the area captured by a 9SF montage. In an exploratory analysis of a subset of study eyes, a single 200 degree Optos FA image captured 1.50x (range 0.71–2.95x) the area captured by montage photography.

Discussion

This comparison of 9-field montage FA images with Optos FA images suggests that more retinal vascular pathology is seen with Optos FA in uveitis patients. Optos FA may be more sensitive than montage FA imaging in the detection of retinal vascular leakage. Two patients in this small series who would have been otherwise assumed to have no angiographic activity were found to have activity with the benefit of Optos imaging. The agreement between the two modalities, for the simple presence or absence of leakage, was very good (Kappa=0.91, 95% CI 0.78–1.03). Nevertheless, the purpose of this study was to assess the difference in the severity and amount of leakage between the two modalities. Indeed, we found that Optos demonstrated a significantly greater area of leakage (median 22.5 mm² vs. 4.8mm²).

We find that there are two primary reasons that more leakage is seen on Optos FA: 1) greater width of field, and 2) the SLO's greater sensitivity for detection of leakage throughout the image field. The existing literature on Optos imaging emphasizes the additional peripheral pathology that can be documented with the wide field images.^{2, 5–8} However, we present preliminary evidence that more leakage is detected with Optos images because of differences in image quality. Simple adjustment for contrast, as we performed in this series, does not neutralize this effect. The SLO overcomes many limitations of a fundus camera's coaxial imaging system including the diffuse illumination provided by a fundus camera's light source. The scanning laser allows the SLO to obtain data point by point, and its detection apparatus suppresses light that is not emanating from the target focal plane. Background fluorescence and stray light is therefore reduced in Optos FA images, and subtle vascular leakage can be more readily imaged.⁹ This can be particularly helpful in detecting small vessel leakage. Furthermore, peripheral images from the fundus camera system tend to be defocused because of astigmatism of oblique incidence. The Optos system does not usually require extreme positions of gaze.

The clinical significance of Optos FA and widefield imaging in uveitis has been assessed previously.^{1, 5, 10} Campbell and colleagues found that widefield Optos FA, when compared with Optos posterior pole FA images, influenced a treatment decision in nearly a third of patients in their series of 43. Eleven eyes (22.4%) in our series had peripheral retinal vascular leakage with no posterior pole leakage. This group of eyes is similar to the group identified by Campbell et al; when image quality is considered, as in the current study, another group with previously unseen pathology is identified.

Peripheral pathology can frequently be detected with montage imaging, but montage imaging requires more technical expertise and patient cooperation and may not be possible in the presence of a small pupil or other media opacities. Furthermore, if the retinal vascular pathology is multifocal, wide angle transit images can show multiple sites. If peripheral foci of leakage are captured only in late montage shots, the underlying lesion can be obscured by a cloud of fluorescein. A potential disadvantage of Optos imaging, as seen in the eyes in this series with less leakage on Optos photos, is obscuration of the superior or inferior retina by the eyelids or cilia.

Although a single Optos FA image captures just 1.09 times the retinal surface area of a 9SF montage as assessed on an artificial eye, an Optos image has greater value in actual practice. In our random sample of ten uveitic eyes, a single Optos image showed 1.50 times the retinal surface area. While our photographers aimed to obtain a full 9-field montage image on each of these 52 eyes, some montages had significant field overlap or captured less than 9 fields because of limited patient cooperation, small pupil, media opacity, or other technical impediments. Because the eye can be rotated to show even more surface area with multiple Optos photos (an "Optos montage"), the imaging capability is probably even greater than this 1.50x figure. While Optos imaging has been shown to aid in assessment of other retinal vascular diseases, its utility in uveitis may be especially important.

Integrating Optos imaging into clinical practice poses some special challenges. While we are able to see subtle inflammatory activity that was previously missed, the practical significance of such findings remains to be determined. Comparing Optos fluorescein images to conventional images is often clinically problematic because the Optos tends to make retinal vascular leakage look worse. For this reason, we have adopted the practice of obtaining conventional montage imaging and late Optos photos. This approach is not practical in many clinical settings but provides better continuity when comparing with historical photos. The addition of Optos FA led to treatment changes in three cases in this series.

There are several limitations to this study. First, the timing of the images may have an impact on the amount of leakage seen. However, our experience suggests that this effect is small and would not begin to account for the 4.7 fold difference in area of leakage. Widefield imaging in the reverse order (Optos transit and late images followed by fundus camera montage imaging) yields very late fundus camera images that are of poor quality, and despite the reversed order the Optos images still reveal more leakage. Second, our analysis can at best be described as semi-quantitative because of the inherently subjective task of measuring areas of fluorescein leakage. While we aligned the majority of our images to address the issue of peripheral image distortion, we have not fully accounted for such distortion.

Previous papers comparing Optos and fundus camera fluorescein angiography have simply simulated fundus camera images and thereby missed image quality differences between the two technologies. Our data is important for confirming the clinical problem we observed while trying to integrate Optos FA into our practice: many of our patients appeared to have

more retinal vascular leakage. It is important for the clinician who is attempting to integrate Optos imaging to have an awareness of this difference and to carefully consider any related management decisions. Future treatment trials using Optos FA imaging will help determine what impact this technology should have on management decisions.

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References

1. Kaines A, Tsui I, Sarraf D, Schwartz S. The use of ultra wide field fluorescein angiography in evaluation and management of uveitis. *Semin Ophthalmol*. 2009; 24(1):19–24. [PubMed: 19241287]
2. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina*. 2012; 32(4):785–91. [PubMed: 22080911]
3. Spaide RF. Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. *Retina*. 2011; 31(5):829–37. [PubMed: 21487338]
4. Anderson, DC.; Lucas, RA.; Henderson, R., inventors. Optos Public Limited Company, assignee. Wide field scanning laser ophthalmoscope. US patent. 5815242. 1998.
5. Campbell JP, Leder HA, Sepah YJ, et al. Wide-field Retinal Imaging in the Management of Noninfectious Posterior Uveitis. *Am J Ophthalmol*. 2012; 154(5):908–11. e2. [PubMed: 22935598]
6. Prasad PS, Oliver SC, Coffee RE, Hubschman JP, Schwartz SD. Ultra wide-field angiographic characteristics of branch retinal and hemisentral retinal vein occlusion. *Ophthalmology*. 2010; 117(4):780–4. [PubMed: 20045570]
7. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol*. 2012; 96(5):694–8. [PubMed: 22423055]
8. Cho M, Kiss S. Detection and monitoring of sickle cell retinopathy using ultra wide-field color photography and fluorescein angiography. *Retina*. 2011; 31(4):738–47. [PubMed: 21836403]
9. Sharp PF, Manivannan A, Xu H, Forrester JV. The scanning laser ophthalmoscope--a review of its role in bioscience and medicine. *Phys Med Biol*. 2004; 49(7):1085–96. [PubMed: 15128191]
10. Tsui I, Kaines A, Schwartz S. Patterns of periphlebitis in intermediate uveitis using ultra wide field fluorescein angiography. *Semin Ophthalmol*. 2009; 24(1):29–33. [PubMed: 19241289]

Figure 1. Aligned, adjusted Optos and montage fluorescein angiogram images used for measurement of retinal vascular leakage in an eye with uveitis
 (Top left and top right) The montage and Optos FA images from this eye with uveitis have been aligned using I2K and contrast-adjusted with Image J. (Middle left and right) Aligned and adjust images were then used to measure the area of FA leakage, which has been outlined here using Image J. Note that more FA leakage is seen in the Optos image than in the montage image. (Bottom left and right) The measured area of leakage is blocked out for emphasis

Figure 2. Comparison of a posterior pole late fluorescein angiogram image from a fundus camera with a posterior pole image from the Optos from the same eye with uveitis
A posterior pole late FA image from a fundus camera (left) is compared with a posterior pole late image from the Optos (right, cropped 200 degree image) in an eye with uveitis.

Note that more FA leakage is seen on the Optos image taken in the same sitting as the fundus camera image.