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Original Research

PERIPHERAL LESION FINDING DISCREPANCIES BETWEEN ULTRA-WIDEFIELD AND SIMULATED 50° FLUORESCEIN ANGIOGRAPHY IN UVEITIS

Rina Wulandari[1], Rina La Distia Nora[1], Lukman Edwar[1]

[1]*Ophthalmology Department, Dr. Cipto Mangunkusumo National Central Hospital University of Indonesia*

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Corresponding author:
Rina Wulandari
Ophthalmology Department, Dr. Cipto Mangunkusumo National Central Hospital University of Indonesia
rinawulandari0202@gmail.com

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ABSTRACT

Introduction: With the advance of ultra-widefield fundus imaging, its usefulness for fluorescein angiography study compared to the conventional (50°) for uveitis management is not fully studied. We aimed to compare ultra-widefield fluorescein angiography (UWFFA) and simulated conventional (50°) FA in terms of peripheral fundus findings and its correlation with clinical activity and therapeutic decision changes in uveitis cases.

Methods: We performed a descriptive retrospective study in uveitis patients who underwent UWFFA (Optos P200DTx California) in March-May 2021. We compared the presence of peripheral abnormalities between UWFFA images and its simulated 50° FA. We correlated them with clinical uveitis activities and therapeutic decision changes by two uveitis experts.

Results: We included 12 uveitis patients and found that 44.4% of peripheral vascular leakage, 83.3% of the peripheral lesion, and 100% of peripheral neovascularization in UWFFA were missed in simulated 50° FA. From 5 clinically inactive patients, 4 out of 5 were assessed as active uveitis on simulated 50° FA interpretation, and all the inactive patients were active uveitis based on UWFFA. 1 out of 12 had a diagnosis and therapeutic changes after UWFFA.

Conclusions: We found more peripheral findings in UWFFA than in conventional ones. This discrepancy could alter clinical activity and therapy decisions, and long-term studies are needed to assess the clinical benefit.

Keywords: fluorescein angiography, ultra-widefield fluorescein angiography, simulated 50° fluorescein angiography, uveitis, peripheral finding

Introduction

Uveitis is an important cause of blindness. The incidence of blindness due to uveitis reaches 30,000 cases each year which constitutes 10-15% of total blindness in the United States of America.[1] This number varies in each geographic area and the prevalence tends to be higher in developing countries. In 2002, there were 38 cases per 100.000 population in France, 200 cases per 100.000 in the United States, and 730 cases per 100.000 in India.[2] Standard uveitis management requires the recognition of anatomical involvement and the grades of inflammation activity. Besides doing clinical examinations to evaluate anatomical classification and grading systems, imaging modalities such as fundus photography and fluorescein angiography (FA) give essential information due to their capability of evaluating retinal blood circulation.[3] Performing the FA procedure on a conventional fundus photography device with a 50° field of view (50° FA) can distinguish between active and inactive uveitis, which often cannot be detected in the usual clinical examination. The FA procedure could detect retinal vasculature leakage, one of the main signs of active uveitis. In addition, FA could detect other pathologies that may accompany uveitis, such as cystoid macular edema (CME), retinal vasculitis, neovascularization, and ischemic areas at the same time.[4,5]

Since 2000, fundus photography has allowed a wider field of view with the ultra-widefield (UWF) system that can document a 200° fundus. UWF fundus photography can also accompany FA examination, known as ultrawide-field fluorescence angiography (UWFFA). UWFFA allows the examiner to get a much wider view than the conventional 50° fundus photography, which is thought to be better at assisting the examiner.[6] As the presence of leakage in the FA is one of the markers of active uveitis. As many as 27% of uveitis cases had peripheral vascular leakage (PVL) in UWFFA, but it was not detected in the conventional 50° FA examination.[3] There were 44.4% of anterior uveitis cases with PVL on UWFFA examination but were found to be inactive on clinical examination.[7]

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Methods

Patient and Data Collection

In this retrospective study, we collected clinical data from uveitis patients who underwent UWFFA between March 1, 2021, and May 31, 2021, in the Division of Infection-Immunology, Ophthalmology Department, Dr. Cipto Mangunkusumo National Central Hospital, Jakarta, Indonesia. We recorded baseline data such as age, sex, diagnosis, and clinical uveitis activity from the medical record and noted the diagnosis and treatment changes after UWFFA performance.

We collected imaging data of the patients from the UWFFA device Optos P200DTx. Then we excluded the inadequate image that obstructs an adequate evaluation (for example, covered central field by eyelid).

UWFFA and Simulated FA 50° Acquisition

One author (RW) did all the image acquisitions and collected three pages of images per patient. Each page for each phase contains six images. The first page was the early phase, collected in less than 60 seconds after fluorescein dye injection, with ±10 seconds intervals. The second page was the mid-fully perfused phase, 60-90 seconds after injection, with ±5 seconds interval. The third page was the late phase, 7-10 minutes after injection, with ±30 seconds intervals. Next, RW simulated all the pages to become the conventional ones, 50° field, completed with written time frame description as shown in the previous UWFFA images.

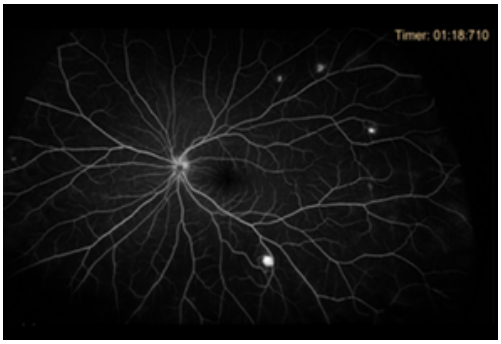

Figure 1. One of the UWFFA images

After randomization and blinding, two uveitis experts from the Division of Infection and Immunology (LE and RLDN) independently interpreted the images from each patient, including both UWFFA and simulated 50° images. The images were reviewed separately and at different times. Interpretations were recorded on a standardized data collection form and subsequently compared between reviewers. The experts evaluated fluorescein leakage patterns, lesion location, and peripheral findings, and determined uveitis activity based on fluorescein angiography. In cases of disagreement, a consensus was reached through discussion.

We classified fluorescence lesions as hyperfluorescent (autofluorescence, staining, leakage, pooling, window defect) and hypofluorescent lesions (blockage, vascular filling defect). Locations were divided into papillary (optic nerve head area), central (macular and or inside vascular arcade), peripheral (outside vascular arcade), and diffuse (involving more than 50% of retinal vasculature).

The experts had interobserver agreement to assess and document peripheral findings consisting of PVL, ischemia, lesion, neovascularization, and exudate, also to interpret uveitis activity based on FA. All processes were done for both UWFFA and simulated 50° images separately.

Analysis

We performed a comparative test in activity diagnostic performance of UWFFA and simulated 50° compared to clinical activity using the McNemar test in IBM SPSS 26.0, with a P value less than 0.05 considered statistically significant.

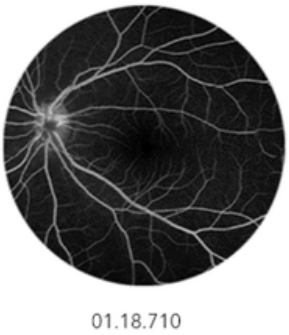

Figure 2. Simulated 50° FA of the same UWFFA image

Results

Baseline Characteristic

We included 12 eyes from 12 different patients with uveitis who underwent UWFFA. One eye per patient was included in the analysis, regardless of the type of uveitis or whether the disease presentation was unilateral or bilateral. It consists of 8 males (66.7%) and four females (33.3%), with a mean age was 35.5 years old (range 17-66 years old). Most cases had unilateral involvement (7 patients; 58.3%). The most diagnosis by anatomic location was panuveitis in 5 patients (41.7%), followed by posterior uveitis in 4 patients (33.3%), intermediate uveitis in 2 patients (16.7%), and anterior uveitis in 1 patient (8.3%).

As many as 7 patients were clinically active (58.3%), and the rest 5 (41.7%) were clinically inactive uveitis. The most common etiology was infection (7 patients; 58.3%), followed by undetermined causes (4 patients; 33.3%), and non-infection (1 patient; 8.3%) who had Vogt-Koyanagi-Harada disease. Infection pathogens were toxoplasmosis in 2 out of 7 patients (28.5%), tuberculosis (TB) in 2 patients (28.5%), cytomegalovirus in 1 patient (14.2%), and rubella virus in 1 patient (14.2%) (Table 1).

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Table 1. Patient characteristic

Variable		Patient (n)(percentage)
Laterality	Unilateral	7/12 (58,3%)
	Bilateral	5/12 (41,7%)
Location	Anterior uveitis	1/12 (8,3%)
	Intermediate uveitis	2/12 (16,7%)
	Posterior uveitis	4/12 (33,3%)
	Panuveitis	5/12 (41,7%)
Clinical activity	Active	7/12 (58.3%)
	Inactive	5/12 (41,7%)
Etiology	Undetermined	4/12 (33,3%)
	Non-infection	1/12 (8,3%)
	Infection	7/12 (58,3%)
	Masquerade syndrome	0/12 (0%)
Pathogen (infection)	Toxoplasma	2/7 (28,5%)
	Tuberculosis (Tb)	1/7 (14,2%)
	Cytomegalovirus (CMV)	1/7 (14,2%)
	Rubella virus	1/7 (14,2%)
	Candida sp.	2/7 (28,5%)

Interpretation of Uveitis Activity with Simulated 50° FA and UWFFA

On simulated 50° FA interpretation, the experts concluded 10 active (83.3%) and 2 inactive (16.7%) cases. Meanwhile on UWFFA interpretation, active and inactive cases were 11 patients (91.7%) and 1 patient (8.3%) respectively.

Comparison of Peripheral Findings in UWFFA and simulated 50° FA

We evaluated five substances of peripheral findings. Later, 44.4% of PVL was detected on UWFFA but was not found in simulated 50°. We also found discrepancies in 83.3% of the peripheral lesion and 100% of peripheral exudates, which were only found on ultra-widefield systems but were absent on conventional ones. Peripheral ischemia and exudate were seen in 1 patient on UWFFA and simulated 50° FA (Table 2).

Table 2. Percentage of eyes (patients) with peripheral angiographic lesions on UWFFA that missed on simulated 50°F

Peripheral findings	FA50°	UWFFA	Percentage of missing findings
PVL	5	9	44.4%
Ischemia	1	1	0%
Lesion	1	6	83.3%
Neovascularization	0	1	100%
Exudate	1	1	0%

Corresponding Alteration of UWFFA Procedure

As previously written, PVL can be missed on simulated 50°FA compared to UWFFA, in which PVL is one of the signs of active uveitis. This study also showed larger discrepancies in FA interpretation compared to clinical activity. There were five clinically inactive patients in this study; later, by simulated 50° interpretation, 4 out of 5 were considered active. Meanwhile, by UWFFA interpretation, all those clinically inactive patients (5 out of 5) were found as active cases. As many as 80% of simulated 50°FA interpretation and 100% of UWFFA interpretation had differences in clinical activity conclusion. In addition, diagnosis and treatment alteration after UWFFA happened in 1 out of 12 patients (8.3%).

Description of simulated FA 50° findings compared with clinical activity of uveitis

The comparison showed 85.7% sensitivity and 20% specificity, with 60% positive predictive value (PPV) and 50% negative predictive value (NPV). Likelihood ratio positive (LR(+)) and negative (LR(-)) values were 1.07 and 2.065, respectively (Table 3).

Table 3. Descriptive test of sensitivity and specificity of simulated FA 50° findings compared to uveitis clinical activity

Interpretation of simulated FA 50°	Uveitis clinical activity		Total
	Active	Inactive	
Active	6 (a)	4 (b)	10 (a+b)
Inactive	1 (c)	1 (d)	2 (c+d)
Total	7 (a+c)	5 (b+d)	12 (a+b+c+d)

Sensitivity : a/(a+c) = 6/7= 85.7%
Specificity : d/(b+d) = 1/5= 20%
Positive Predictive Value (PPV) : a/(a+b) : 6/10 = 60%
Negative Predictive Value (NPV) : d/(c+d) = 1/2= 50 %
Likelihood Ratio (LR (+)) : sensitivity/(1-specificity) = 0,857/0,8= 1,07
Likelihood Ratio (LR (-)) : (1-sensitivity)/specificity = 0,143/0.2 =2,065

Description of UWFFA findings compared with clinical activity of uveitis

The sensitivity had a similar value to the previous comparation, which was 85.7%, but 0% of specificity. The PPV was 54.5% and 0% of negative predictive value (NPV). LR (+) value was 0.857 and 0 for NPV (Table 4).

Activity Diagnostic Performance

We conducted a statistical test to determine activity diagnostic performance of UWFFA and simulated FA50°compared to clinical activity (gold standard). Simulated FA50° had 0.682 (Fisher's exact), and UWFFA had 0.583 (Fisher's exact) value. Both had p>0.05 and were considered statistically insignificant.

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Table 4. Descriptive test of sensitivity and specificity of UWFFA findings compared to uveitis clinical activity

Interpretation of UWFFA	Uveitis clinical activity		Total
	Active	Inactive	
Active	6 (a)	5 (b)	11 (a+b)
Inactive	1 (c)	0 (d)	1 (c+d)
Total	7 (a+c)	5 (b+d)	12 (a+b+c+d)

Sensitivity : a/(a+c) = 6/7= 85.7%
Specificity : d/(b+d) = 0/5= 0%
Positive Predictive Value (PPV) : a/(a+b) : 6/11= 54.5%
Negative Predictive Value (NPV) : d/(c+d) = 0/1= 0 %
Likelihood Ratio (LR (+)) : sensitivity/(1-specificity) = 0,857/1= 0.857
Likelihood Ratio (LR (-)) : (1-sensitivity)/specificity = 0,143/0 = 0

DISCUSSION

This study showed more peripheral pathological findings in UWFFA than the simulated 50° images and changed the decision of clinical activity diagnosis and therapeutic plan. As many as 44.4% of PVL was detected on UWFFA but was not found in simulated 50°, also happened in detecting 83.3% peripheral lesion and 100% of peripheral exudates, meanwhile peripheral ischemia and exudate finding did not show any differences on those two versions of FA. This type of results was also shown in a study of peripheral abnormality by Pecen et al., that PVL, ischemia or non-perfusion area, lesion, neovascularization and exudates were missed on simulated 50° with percentages of 27%, 14%, 6.6%, 3.9% and 3.1% respectively.[3] Differences were not found in peripheral ischemia and exudate finding result, due to small sample size in this study.

The SUN system determined the active state of uveitis inflammation activity as presenting of anterior and or vitreous cells.[3] In addition, experts are often use CME as a predictor of uveitis activity.[8] The incidence of uveitis often involves retinal vasculature, with arterial and venous involvement in 58.8% of uveitis cases, periphlebitis in 36.5% of cases, and periarteritis in 4.5% of cases. FA is very helpful in the assessment of vascularity and helps to diagnose some typical uveitis, determine the activity state, and to evaluate the therapy response.[9]

PVL is important in uveitis, it gives an opportunity to treat uveitis before CME occurs which can significantly reduce visual acuity.[10] A study by Leung et al., had 156 eyes with retinal vascular disease as subjects, showed that presenting PVL has a high correlation with CME.[11] Furthermore, PVL can also happen in quiescent or inactive anterior uveitis as written on a study by Chi et al. , that 42% (27 of 65 eyes) of quiescent anterior uveitis had PVL on UWFFA and later some of them were having treatment changes due to this result[7] Nicholson et al. in their study, compared UWFFA with conventional 9-field montage FA. Although not completely similar to this study, UWFFA was shown to have more advantages in 49 research subjects, which can detect 25% more leakage in 22 of 49 patients (45%), compared to the montage technique of the conventional one.[13] It is currently believed that the presence of vascular leakage or vasculitis has a better value to assess uveitis activity, with a 95% sensitivity and 93% specificity, is considered as a major impact on uveitis management. [3] Moreover in this study, 44.4% of PVL was detected on UWFFA but was not found in simulated 50°, so that UWFFA notably showed superiority in this utility.

In our study, the uveitis activity conclusion according to the simulated FA50° were compared with clinical examination as the gold standard, yielded that 85.7% of research patients stated as active both on the simulated FA50° and on clinical examination, meanwhile 20% of patients who were inactive on the simulated FA50° were also clinically inactive. If the patient was declared as active according to the FA50° simulation, there was a 60% chance of being clinically active as well. Otherwise, if it was declared as inactive by simulated FA50°, it was also clinically inactive with a probability of 50%. With all those results, it showed that the simulated FA50° has small value in determining both active and inactive uveitis activity.

Meanwhile on UWFFA results, despite the same sensitivity, 85.7% of patients were stated as active on both clinical and by UWFFA interpretation, but none of the patients who were inactive on UWFFA were concluded to be clinically inactive. If the patient was declared as active according to UWFFA, there was a 54.5% chance of these patients also being clinically active, and if it is stated as inactive on UWFFA, the chance to be concluded as clinically inactive was 0%. Later concluded that UWFFA in this study has small value in determining active cases but has large value in determining inactive cases on clinical examination.

The result of this descriptive test was different from the previous study conducted by Pecen et al. who were using 1008 eyes as subject, where the determining activity with UWFFA compared with clinical examination has a fairly high sensitivity and specificity, which were 95 and 93% respectively, with PPV of 95% and NPV of 97%.[3] Our results in the present study were lower, indicating that there were many patients with active states found on simulated 50° FA and UWFFA which were not concluded as active on clinical examination. This situation resulted from the very large gap in the number of research patients, as the present used only 12 patients, but certainly it could not rule out the large benefit of UWFFA.

Similar UWFFA advantages in determining activity state were also given by other several studies. Campbell et al. assessed 43 patients who underwent clinical examination alone, compared with clinical examination with UWFFA and clinical examination with conventional FA. In the clinical examination only-group 44% was clinically active and had 14% treatment changes. Combination with UWFFA found 63% of active states, and treatment changes occurred in 48% patients. This figure is lower in conventional FA, which is 51% and 16% respectively. Even the use of UWF photography, rated better than conventional FA, it was able to detect uveitis activity in 56% of patients, and made treatment changes in 35% of patients.[12] Chi et al. , in his study with 65 eyes of inactive anterior uveitis, 27 of 65 eyes had PVL on UWFFA, 15 out of 27 eyes turned to be considered as clinically active and 12 out of 15 eyes had therapy changes by giving more dose of steroid[7] In the other side, a study by Kang et al., showed quite the opposite, that 37 eyes with anterior and intermediate uveitis with PVL, did not have a correlation with presenting active uveitis cells.[14]

Statistically in our study, there was no discrepancy in diagnostic performance between FA50° and UWFFA compared with clinical examination ($p<0.005$, Fisher's exact test), but in practice, our study showed that of the 5 inactive uveitis patients, 4 of them (80%) were concluded to be opposite (active state) on the FA50° simulation. More significant results occurred in the UWFFA examination, that 5 clinically inactive cases, all cases (100%) turned out to be active on UWFFA. The discrepancy was also important in determining activity for therapy adjustment, where changes in diagnosis and treatment after FA occurred in 1 out of 12 study patients (8.3%). This result showed a significant advantage of UWFFA in daily practice in treating uveitis patients.

In addition, active uveitis on UWFFA can occur in clinically inactive cases without any anterior chamber cells and lower vitreous cells than trace according to SUN grading system. Determining active state based solely on FA cannot be fully carried out at this time and further evaluation is needed. Until recently, experts has not been established a standard in determining activity status only based on angiography.[3]

This study has several limitations. Firstly, the sample size of this study is only 12 patients which is a small sample size. This limits the generalizability of the findings and increases the influence of individual cases on the results. The study design used was retrospective design, which relied on existing clinical records and imaging data this can cause restricted control over data acquisition and may have introduced selection bias and variability in data quality. Finally, there is currently no universally accepted definition of uveitis activity based solely on fluorescein angiography, resulting in a reliance on expert interpretation, which may be subject to interobserver variability.

CONCLUSION

In conclusion, UWFFA reveals more pathology and findings than the conventional 50°FA, and has proven as well assisting tool in uveitis diagnosis, uveitis activity classification and has ability to direct treatment alteration. On the other hand, determining activity should be evaluated comprehensively with clinical examination. Further study with a larger sample may create more objective results in measuring inflammation activity in uveitis cases.

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