Utility of Oral Fluorescein Angiography with Ultra-wide-field Imaging System for Evaluation of Various Retinal Disorders

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Summary Statement

We evaluated the utility of oral fluorescein angiography with the ultra-wide-field imaging system predominantly in pediatric retinal disorders. Image quality was assessed
using various parameters. Most images had sufficient quality to evaluate disease activity making this modality clinically effective especially for children who cannot tolerate intravenous injection.

Abstract

Purpose: To evaluate the utility of oral fluorescein angiography with ultra-wide-field imaging system (oral UWF-FA) predominantly in children.

Methods: We recruited 17 patients aged 2 to 22 years with retinal disorders. Each patient ingested a dose of fluorescein sodium set by body weight mixed with 100 mL of juice. Images were scored using four parameters as follows: branch retinal vessel identification, retinal vessels visualization, foveal avascular zone visualization, and clinically important findings such as leakage, microaneurysms, neovascularization, or significant nonperfusion area visualization. Based on the aggregate score, we classified the image quality into three grades.

Results: Sixteen out of 17 patients completely ingested the fluorescein sodium, and
UWF-FA was performed. Images were classified as high-quality in nine cases, moderate-quality in four, and poor-quality in three. In 13 cases (81.3%), images had adequate quality to evaluate retinal conditions. Out of three patients with poor-quality images, two took 10 minutes to ingest fluorescein sodium and the other ingested only half the dose. The adverse event of a mild skin rash was noted in one patient.

**Conclusion:** Oral UWF-FA is effective in evaluating retinal pathology and is a useful alternative especially for pediatric patients who cannot tolerate intravenous line placement.

**Key Words:** Coats disease; familial exudative vitreoretinopathy; fluorescein angiography; intake of fluorescein sodium; oral fluorescein angiography; pediatric patient; pediatric retinal disorder; ultra-wide-field imaging system; uveitis

**Introduction**

The ultra-wide-field (UWF) imaging system has been widely used as a retinal image
evaluation device. The UWF imaging system can image 200° of the retina in a single
image in 0.4 seconds. It is also capable of fluorescein angiography (FA) transiting the
same 200° area, which is useful for evaluating not only for posterior retinal conditions
but also for the peripheral retinal conditions.

Recently, the optical coherence tomography angiography (OCTA) has been developed
and is gaining popularity. One major reason for this popularity is that it does not require
intravenous fluorescein sodium, which has potential adverse effects, such as nausea,
vomiting, venipuncture, extravasation, and life-threatening anaphylactic shock.

However, currently, OCTA has several limitations, including narrow-field imaging and
inability to evaluate the leakage from neovascular vessels. Therefore, it is unrealistic
that FA can be eliminated from our daily clinical practice, especially in the evaluation of
neovascular ocular diseases, such as diabetic retinopathy, retinal vein occlusion, and
age-related macular degeneration.

In pediatric retina practice, FA is useful in evaluating disease activity of various
diseases, such as retinopathy of prematurity, familial exudative vitreoretinopathy, and
Coats disease. However, pediatric patients often do not cooperate with FA, as it requires administration of intravenous dye. FA with oral intake of fluorescein sodium (oral FA) has been proposed as an alternative to FA with intravenous injection of fluorescein sodium (IVFA).\textsuperscript{1-4} Oral FA produces inferior quality images with a conventional fundus camera,\textsuperscript{2-4} however, using a scanning laser ophthalmoscope (SLO) solves the problem.\textsuperscript{5-7} The UWF imaging system also uses the SLO with a higher sensitive camera. Recently, while UWF-FA with intravenous injection of fluorescein sodium (UWF-IVFA) has been widely reported,\textsuperscript{8-9} there have been only a few reports on the use of oral UWF-FA.\textsuperscript{10-12}

We report our oral UWF-FA experiences predominantly in pediatric patients with various retinal disorders.

\textbf{Materials and Methods}

\textbf{Patient selection and characteristics}

This study was conducted from July 2014 to January 2019 at Kindai University
Hospital and adhered to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Kindai University Faculty of Medicine (#25-202). Oral FA involves off-label usage of fluorescein sodium. Hence, the first choice of FA during the study period was IVFA. We explained in detail about oral FA and IVFA to patients and their parents or guardians who were not likely to be cooperative for IVFA and or who refused IVFA mainly because of the placement of a painful peripheral venous infusion line, and the decision to choose was left to them.

Written informed consent was obtained from all the adult patients and parents or guardians of minors.

Seventeen patients ranging in age from 2 years and 11 months to 22 years were recruited in this study. There were 11 boys, five girls, and a 22-year-old man. Eleven of 17 patients (65%) were 6 years old or younger. Except for a 22-year-old man, all the other patients were 12 years old or younger. Clinical diagnoses included 10 cases of familial exudative vitreoretinopathy (FEVR), five cases of Coats disease, one case of uveitis, and one case of cytomegalovirus retinitis. Two cases of a 22-year-old man with
FEVR and a 10-year-old boy with cytomegalovirus retinitis had an adverse event history of nausea upon previous intravenous injection of fluorescein sodium.

For evaluations of treatment for the diseases, three cases received oral UWF-FA twice, before and after treatment.

**Oral fluorescein sodium intake and angiography protocols**

The patients’ pupils were pharmacologically dilated before imaging was performed. Ultra-Wide field SLO (Optos® California or 200Tx, Optos plc., Dunfermline, Scotland, United Kingdom) was utilized for noncontact high-resolution retinal angiograms. Approximately 25 mg/kg of 10% fluorescein sodium (Fluorescite®, Novartis Pharma, Basel, Switzerland) was mixed with 100 ml of fruit juice. The patients were instructed to ingest the fluorescein sodium as quickly as possible. Two patients who had nausea previously due to intravenous injection of fluorescein sodium were given 15 mg/kg of 10% fluorescein sodium with 100 ml of juice. When patients completed the full dose of fluorescein sodium, the imaging system timer was started. The images were obtained
every minute until the late arteriovenous phase was reached, and then, every 5 minutes until the late phase was reached.

**Image analysis**

For quantitative evaluation of the utility of oral UWF-FA, the image quality scoring was done by five experienced retina specialists. They were blinded to the patients’ clinical information and performed the scoring independently. To score the images, we used four different image quality parameters, which were modified from the methods previously used by Amador-Patarroyo, Squirrel, and Garcia et al.\textsuperscript{5-7} The four parameters were (A) the branch retinal vessel identification, (B) the retinal vessels visualization, (C) the foveal avascular zone (FAZ) visualization, and (D) the clinically important findings, such as the absence or presence of leakage, microaneurysms, neovascularization or significant nonperfusion area visualization. In the scoring of (B), (C) and (D), each observer used the UWF-IVFA images obtained in usual clinical practice as comparisons for the oral UWF-FA images. All the parameters were scored
using a three-point scale as follows, (A): 0 points; first-order branch not seen, 1 point; only first-order branch seen, 2 points; second-order branch or more seen, (B): 0 points; poor, 1 point; intermediate, 2 points; equivalent to images by UWF-IVFA, (C): 0 points; impossible to judge, 1 point; seen but not clearly, 2 points; seen equivalent to images by UWF-IVFA, and (D): 0 points; impossible to judge, 1 point; seen but not clearly, 2 points; seen equivalent to images by UWF-IVFA. Depending on the fundus findings, FAZ may not be determined regardless of methods of fluorescein sodium administration.

Therefore, in the scoring of (C), we selected a better score for each of the right and left eyes. For all parameters, we calculated interobserver agreement using the kappa statistic.

Kappa values were interpreted as follows: < 0.00, poor agreement; 0.00-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement.

We evaluated the sum of each score as an indicator of image quality. To evaluate the image quality based on the score of each parameter, all observers were asked about the score of each parameter needed for the images to be clinically useful. All of them
answered that (A) required 2 points, and (B), (C) and (D) required 1 point for them to judge the clinical retinal conditions from the images. Based on their answers and the total score of each image, we classified the images into the following three grades. The image with a maximum of 8 points was defined as high-quality, which had almost equivalent quality as that of images by UWF-IVFA. The total score required for the clinically useful quality determined by all observers was 5 points or more. Therefore, total score of 5, 6 and 7 points were defined as moderate-quality, and 4 points or less as poor-quality. Even if one parameter score had zero points, the image was classified as poor-quality.

Statistical analysis

Interobserver agreement was assessed using the kappa statistics. For multiple observers, we calculated the kappa values for pairs of observers and then computed an average kappa value for all possible pairs. Statistical analysis was performed using JMP version 13.0 software (SAS Institute Inc., Cary, NC).
Results

Patients characteristics

The characteristics of the 17 cases are shown in Table 1. Sixteen out of 17 cases were able to ingest the fluorescein sodium. A 10-year-old boy with cytomegalovirus retinitis (case 17) denied because of the bitter flavor of fluorescein sodium. In the other 16 cases, oral UWF-FA was performed. In cases 14 and 15, however, it took more than 10 minutes for ingestion of the full fluorescein sodium despite being instructed to ingest it as quickly as possible. Case 14, the youngest girl, 2 years and 11 months, co-operated for UWF-FA. We did not hold her during the examination because could put her chin on the chin-rest according to our instruction.

Image quality analysis

Of the four parameters used for scoring, for (A), all observers gave 2 points in all cases. The scores for the other three parameters varied within 1 point between observers.
Figure 1 shows representative images of each score of (B), (C) and (D) parameters.

Out of the 16 cases who completed oral UWF-FA, nine cases were classified as high-quality, four were moderate-quality, and three were poor-quality (Table 1). In nine out of 16 cases (56.3%), obtained images were judged to be equivalent to images of UWF-IVFA. In 13 out of 16 cases (81.3%), obtained images were judged to be clinically useful. Figure 2 shows representative images of case 2 with FEVR classified as high-quality, to which all observers gave perfect scores. The peripheral nonperfusion area with leaking telangiectatic vessels in the temporal peripheral retina is clearly visible.

Three cases (cases 14, 15, and 16) were classified as poor-quality. Two out of the three cases (cases 14 and 15) took more than 10 minutes for ingestion of the fluorescein sodium. Figure 3 shows images of case 15 with FEVR classified as poor-quality. Images obtained at 50 minutes post oral intake showed low contrast due to which it was difficult to evaluate the disease activity accurately. Further, case 16 classified as poor-quality was administered half a dose of fluorescein sodium as compared to the
others, because of a history of nausea at the previous IVFA. Figure 4 compares images obtained by UWF-IVFA and oral UWF-FA. The total score using our scoring system for UWF-IVFA and oral UWF-FA were 5~7 and 2~4 points, respectively. Apparently, in this particular case with half-dose oral fluorescein sodium, the quality of oral UWF-FA images was inferior to that of UWF-IVFA.

**Reproducibility of the image quality**

We performed oral UWF-FA twice, before and after surgery, in three cases (cases 2, 3 and 4). In two out of the three cases, images were classified as high-quality both in the first and the second time. Figure 2 shows the images before and after the operation in case 2. Both images were classified as high-quality and sufficiently useful for evaluating disease activity. On the other hand, in case 4, all observers gave the first images a maximum of 8 points, while they gave the second images a total score of 5 points. Figure 5 shows the images obtained at the first and second oral UWF-FA in case 4. In the first examination, he could ingest the fluorescein sodium in one gulp, while it
took 5 minutes in the second one.

**Interobserver agreement**

The Kappa values of each parameter were 1.00 for parameter (A), 0.90 for (B), 0.59 for (C), and 0.59 for (D). Overall, interobserver agreement was moderate to almost perfect for all parameters. Among all observers, the grading state by total score was consistent in all cases.

**Phase wise vascular visualization following oral intake**

We recorded the time interval between oral intake and the first image which showed the presence of fluorescein sodium in the major retinal vessels (Table 1). In all patients, except in patients 14 and 15 where the images were classified as poor-quality, the first images were obtained as early as 4 minutes and as late as 8 minutes after oral intake. The choroidal flush was not appreciated. Following the first images, the late arteriovenous phase was visible, and the recirculation phase was visible no later than 17
minutes after oral intake. On the other hand, in patients 14 and 15 where it took more than 10 minutes for ingestion of the fluorescein sodium, it took 30 minutes for fluorescein to be first visible, and subsequent gradual observation of the image was difficult due to poor image quality.

**Adverse events**

An adverse event of mild skin rash, which resolved spontaneously after about an hour, in patient 16 who had a history of nausea was caused by the previous IVFA. In other cases, there were no adverse events following oral UWF-FA.

**Discussion**

In this study, we showed that oral UWF-FA was clinically useful for diagnosis and management of pediatric retinal disorders. In more than 80% of our cases, images with quality sufficient to evaluate the disease condition were obtained. To the best of our knowledge, this study is the first one to quantitatively evaluate the utility of oral
UWF-FA in pediatric disorders. Especially for pediatric patients, oral intake of fluorescein sodium is more advantageous than conventional intravenous administration, as the former does not require placing a painful peripheral venous infusion line. This can reduce not only the patients’ risk and discomfort but also labor and burden of the medical staff.

In order to obtain clinically useful image quality with oral FA, we consider a couple of points to be important. First, the UWF imaging system should be used. It is equipped with a highly sensitive detector specialized for emission light of a fluorescein dye. Therefore, with UWF-FA, we can obtain higher quality images than images with a conventional fundus camera equipped with a conventional detector for light with a wide range of wavelengths. Second, the patients should ingest the appropriate dose of fluorescein sodium in a short time, ideally in one gulp. In our cases who did that, images had sufficient quality for diagnosis and management of typical pediatric retinal diseases, such as FEVR, Coats disease, and uveitis. Regarding the dose of fluorescein sodium, 25 mg/kg of body weight according to previous reports was administered.
In consideration of the bitter taste of fluorescein sodium, we mixed it with 100 ml of fruit juice. Although the concentration of fluorescein sodium in our study was lower than that of previous reports in which it was mixed with 30 ml of juice,\textsuperscript{5,10,11} we could obtain clinically useful information in most cases. The time to obtain the first images was approximately the same as previously reported.\textsuperscript{5,10,11} On the other hand, as shown as Figure 4, in case 16 in which the dose of fluorescein sodium was half, all the images were considered as poor-quality. Figure 5 shows images of case 4, in which oral UWF-FA was taken twice, before and after laser treatment. The image quality obtained in the first and second examinations was clearly different. In the second examination, where the image quality was poor, the patient took longer for ingestion of the fluorescein sodium. Similarly, in cases 14 and 15, oral intake of fluorescein sodium took about 10 minutes, and the images were classified as poor-quality. From these results, we consider that it is important to ingest the appropriate dose of fluorescein sodium in one gulp to ensure the required image quality with oral UWF-FA.

In FA, vascular phase wise demarcation of choroidal and retinal circulation is one of
the important factors for diagnosis or management of diseases. In our oral UWF-FA examination, the first images were the arterial phase or the arteriovenous phase. The choroidal flush was not appreciated in all cases. It was difficult to distinguish the classical FA phases as clearly as IVFA, probably due to the slow increase of the fluorescein sodium concentration compared to IVFA. However, the visualization of gradual changes of clinically important findings such as leakage, microaneurysms, and nonperfusion areas was quite possible as shown as Figure 6.

It is generally assumed that the adverse reaction rate and severity is lesser with oral intake than with intravenous injection. No severe adverse events have been previously reported following oral FA. In our study, an adverse event occurred only in case 17. The patient had only a mild skin rash, while nausea was seen with the previous IVFA. No other adverse events were seen in other patients. However, because of the small number of patients in this study, it is impossible to evaluate the safety of oral FA from our results.

Oral UWF-FA has some disadvantages. First, it involves off-label usage of fluorescein
sodium and requires institutional review board approval. It is necessary to consider the cost-benefit ratio according to the medical insurance system in each country. Second, if the patients cannot tolerate oral intake of the fluorescein sodium, the examination cannot be performed. Third, it is difficult to obtain information on indicators of ocular circulation, such as choroidal flush and arm-to-retina circulation time, and to distinguish the classical FA phases as clearly as IVFA. Therefore, oral UWF-FA is not likely to replace IVFA. However, considering the advantages mentioned above, we believe that it is a useful, convenient mode of examination, and an alternative to IVFA, especially for pediatric patients who are uncooperative with intravenous line placement and have difficulty concentrating for a long time during the examination.

In conclusion, our study showed that most images obtained by oral UWF-FA were clinically useful. Although this method will not replace IVFA, it is a useful alternative with equivalent image quality to IVFA, especially for pediatric patients.
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Figure legends

Figure 1: Representative images of each score of parameter (B), (C), and (D).

The representative images of each score of parameter (B), (C), and (D) are shown. Each image was selected from images for which all observers gave the same score.

(B) visualization of the retinal vessels: 0 points; poor, 1 point; intermediate, 2 points; equivalent to images by UWF-IVFA.

(C) the foveal avascular zone (FAZ) visualization: 0 points; impossible to judge, 1 point; seen but not clearly, 2 points; equivalent to images by UWF-IVFA.

(D) clinically important findings, such as the absence or presence of leakage, microaneurysms, neovascularization, or significant nonperfusion area, visualization: 0 points; impossible to judge, 1 point; seen but not clearly, 2 points; equivalent to images by UWF-IVFA.

Figure 2: Images of case 2 (a 4-year-old girl with familial exudative vitreoretinopathy).

A: OD before treatment

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B: OS before treatment

C: OD after treatment

D: OS after treatment

All images were classified as high-quality by all observers.

A/B (Before treatment)

Bulbous vascular endings or telangiectasias and supernumerary vascular branching observed at the terminal ends of vessels abutting the vascular-avascular junction.

Peripheral laser scars are visible.

C/D (After treatment)

Additional laser scars are visible at the peripheral nonperfusion area in the images before treatment.

**Figure 3: Images of case 15 (a 4-year-old girl with familial exudative vitreoretinopathy)**

A: OD

B: OS
Both images were classified as poor-quality. The grading scores were as follows: (A) branch identification; 2 points, (B) vessel visualization; 0 or 1 point, (C) FAZ visualization; 0 points, (D) visualization of clinically important findings; 0 or 1 point, and total score was 2, 3 or 4 points. She took 30 minutes to ingest the full fluorescein sodium.

**Figure 4: Images of case 16 (a 22-year-old man with familial exudative vitreoretinopathy)**

A: OD oral UWF-FA  
B: OS oral UWF-FA  
C: OD UWF-IVFA  
D: OS UWF-IVFA  

Both images by oral UWF-FA were classified as poor-quality. The grading scores were as follows: (A) branch identification; 2 points, (B) vessel visualization; 0 points, (C) FAZ visualization; 0 or 1 point, (D) visualization of clinically important findings; 1 point, and total score was 3 or 4 points. The image quality obtained by oral UWF-FA
was inferior to that obtained by UWF-IVFA. The patient was administered half the dose of oral fluorescein sodium as compared to the others because of a history of nausea during a previous UWF-IVFA.

**Figure 5: Images of case 4 (a 6-year-old boy with Coats disease)**

A: OS in the first oral UWF-FA

The image clearly shows leaking microaneurysms in the temporal area with nonperfusion areas. It was classified as high-quality by all observers. The patient ingested the fluorescein sodium in one gulp in the first oral UWF-FA.

B: OS in the second oral UWF-FA

The image was classified as moderate-quality. The grading scores were as follows: (A) branch identification; 2 points, (B) vessel visualization; 1 point, (C) FAZ visualization; 1 or 2 points, (D) visualization of clinically important findings; 1 or 2 points, and total score was 5 points. Compared with the first image, the second image shows a lower contrast. The patient took 30 minutes to ingest the full fluorescein sodium in the second time.
Figure 6: Images of case 3 (a 5-year-old boy with familial exudative vitreoretinopathy).

A: OD 7 minutes after oral intake

B: OD 14 minutes after oral intake

Both images were classified as high-quality by all observers. Prominent temporal vascular dragging, hyperfluorescence, and leakage from neovascularization are clearly visible. It can be appreciated that the leakage from neovascularization increases with time.
Table 1. Summary of 17 cases

| Case No. | Age (year) | Sex | Disease               | Oral intake time of fluorescein sodium | Adverse Event | Images' Total Score | Image Quality | Time to the first image (minutes) |
|----------|------------|-----|-----------------------|---------------------------------------|---------------|---------------------|---------------|----------------------------------|
| 1        | 4          | M   | FEVR                  | in one gulp                            | none          | 8                   | High          | 5                                |
| 2        | 4          | F   | FEVR                  | in one gulp                            | none          | 8                   | High          | 4                                |
| 3        | 5          | M   | FEVR                  | in one gulp                            | none          | 8                   | High          | 6                                |
| 4        | 6          | M   | Coats disease         | in one gulp                            | none          | 8                   | High          | 4                                |
| 5        | 6          | M   | Coats disease         | in one gulp                            | none          | 8                   | High          | 4                                |
| 6        | 6          | F   | FEVR                  | in one gulp                            | none          | 8                   | High          | 8                                |
| 7        | 7          | M   | Uveitis               | in one gulp                            | none          | 8                   | High          | 8                                |
| 8        | 9          | M   | Coats disease         | in one gulp                            | none          | 8                   | High          | 7                                |
| 9        | 10         | M   | Coats disease         | in one gulp                            | none          | 8                   | High          | 4                                |
| 10       | 4          | F   | FEVR                  | in one gulp                            | none          | 6~7                 | Moderate      | 4                                |
| 11       | 5          | M   | FEVR                  | in one gulp                            | none          | 6~7                 | Moderate      | 7                                |
| 12       | 6          | M   | Coats disease         | in one gulp                            | none          | 6~7                 | Moderate      | 4                                |
| 13       | 12         | M   | Coats disease         | in one gulp                            | none          | 5~7                 | Moderate      | 6                                |
| 14       | 2          | F   | FEVR                  | 10 minutes                             | none          | 2~3                 | Poor          | 28                               |
| 15       | 4          | F   | FEVR                  | 10 minutes                             | none          | 2~4                 | Poor          | 30                               |
| 16       | 22         | M   | FEVR                  | half dose in one gulp                  | mild skin rash| 2~4                 | Poor          | 4                                |
| 17       | 10         | M   | Cytomegalovirus retinitis | could not ingest         | -             | -                   | -             | -                                |

M; male, FEVR; familial exudative vitreoretinopathy, F; female
