COMPARISON BETWEEN ORAL AND INTRAVENOUS ULTRAWIDE-FIELD FLUORESCEIN ANGIOGRAPHY IN THE CLINICAL FOLLOW-UP OF CHILDREN WITH A HISTORY OF RETINOPATHY OF PREMATURITY OR PREMATURITY

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Purpose: To compare between oral and intravenous (IV) ultrawide-field fluorescein angiography in pediatric patients with a history of prematurity of retinopathy or prematurity.

Methods: Pediatric patients (<18 year old; n = 107 patients) who underwent ultrawide-field fluorescein angiography for retinopathy of prematurity were categorized into oral and IV fluorescein angiography (FA) groups. Quality of FA images was graded on the order of retinal vessels visible. Reported outcomes were proportions of graded FA images, peak fluorescein intensity, and the time to first dye appearance and to reach peak fluorescence.

Results: Image quality analysis revealed that 91.5% of IV FA images had excellent image quality compared with only 55.6% of oral FA images ($P < 0.01$). There were still 83.3% of oral-contrast images with good or excellent image quality. The average time required for first dye appearance and peak fluorescence were significantly shorter in the IV FA group than in the oral FA group ($P < 0.01$). Peak intensity was greater in the IV group (141.41 ± 29.09) than in the oral group (111.25 ± 45.68; $P < 0.01$). Adverse reaction rates were similar between the two groups ($P = 0.22$).

Conclusion: Ultrawide-field fluorescein angiography provides excellent-quality imaging of the retina in the pediatric population. Overall, oral FA is still an effective and useful alternative to IV FA in children with prematurity history.

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Fluorescein angiography (FA) is routinely used in clinical practice to investigate pathologies involving retinal or choroidal vessels. Conventionally, since it was first described in 1961, administration of fluorescein sodium via the intravenous (IV) route has remained the standard for performing FA examinations.[1] However, this route of administration may be unsuitable for certain populations, including patients who are intolerant to IV access or general anesthesia, particularly children. An alternative method of fluorescein dye administration has thus been proposed through the oral route.[2] Through recent developments, orally administered fluorescein sodium has been proven to be safe and effective in general clinical practice.[3,4] In addition, image quality and diagnostic utility have been shown to improve drastically compared with when the technique was first described.[2,5]

Retinopathy of prematurity (ROP) is characterized by abnormal vascular development because of prematurity factors and is a leading cause of blindness in children

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worldwide.[6] Retinopathy of prematurity is primarily a vascular disease. Better visualization and accurate observation of pathologic new vessels, retinal capillary network, and circulation dynamics, in the acute phase or in long-term clinical follow-up, can be provided via FA. In performing FA for children with ROP during clinical follow-up, noncontact ultrawide-field FA (UWFFA) is preferable because of its 200º field of view, rapid acquisition, and complete fundus imaging.[7] Using oral fluorescein, pediatric patients with a history of ROP can be more readily imaged in an outpatient clinical setting. This provides an efficient and useful tool to investigate the long-term manifestations of the peripheral vasculature of ROP patients.

To date, literature regarding the use of ultrawide-field oral FAs is scarce, especially in the pediatric population.[7–9] There is still no large cohort examining the use of oral FA in long-term outpatient follow-up of the pediatric population with a history of ROP in comparison to IV FA. The clinical applicability, quality of angiographic images, pharmacodynamic information, and standardized protocol of oral FA for pediatric patients remain a concern. To address these issues, the objectives of this study were to compare the image quality of oral and IV fluorescein in UWFFA for clinical utility in the follow-up of the ROP pediatric population and to investigate the test dynamics involved (time required to reach first dye appearance and peak fluorescence, overall image intensity, and adverse reactions).

Methods

Study Population

All pediatric patients (<18 year old) with a history of ROP (nontreated) or treatment (treated with photocoagulation or intravitreal injection) in a single academic tertiary referral center (Chang Gung Memorial Hospital, Linkou, Taiwan) who had UWFFA performed during clinical follow-up between January 1, 2008 and June 15, 2020 were included. Eligible patients had an attached retina during follow-up, no severe congenital defects or cerebral damage limiting FA examination and no previous history of adverse reaction to fluorescein. The study adhered to the tenets of the Declaration of Helsinki and was approved by an institutional review board (IRB) associated with the center (IRB No. 201801566A3).

Fluorescein Angiography Protocol

Parents were educated on the off-label use of oral and IV fluorescein sodium and signed informed consent forms before the procedure. The use of oral fluorescein is considered off-label usage in Taiwan, but was approved by the IRB for use in this study. All families were carefully educated on the benefits and possible risks involved in the use of oral fluorescein sodium. The indications for oral fluorescein included requests from parents because of concerns regarding their children's inability to tolerate venous access and fear of needles.

The oral fluorescein protocol followed previously reported methods with modifications[10,11]: Two ampoules of 10% fluorescein dye (maximum dosage of 25 mg/kg) were mixed with approximately 30 mL of orange juice. The mixture was ingested by the patient. The protocol was previously reported and was also approved by the IRB in our center. Subsequently, noncontact high-resolution ultrawide-field retinal angiographic images were obtained with a dedicated imaging system (P200MA, 2008 and California, 2015; Optos, MA).

Intravenous FA was performed for patients who did not choose oral administration. The standardized protocol comprised a dose of 7.7 mg/kg (maximum dosage of 500 mg) injected via a venous cannula, followed by a bolus flush with normal saline. Any occurrence of adverse reactions was monitored closely and recorded. The overall workflow diagram was shown in Figure 1.

Imaging Analysis

For patients who underwent multiple FAs, only the most recent studies were included for analysis. Two masked retinal specialists were responsible for grading the obtained sets of images based on the visibility of 1) the order of retinal vessel branches and 2) the foveal avascular zone (FAZ). Each set of FA images was randomized and provided to the image graders with removal of patient identifiers. The grading system was standardized and was detailed as follows: visibility of the retinal vessel branch order was defined as 0 (first order branch not visible); 1 (only the first order branch visible); 2 (second order branch visible); 3 (third order branch visible); and 4 (fourth order branch visible). Image quality was considered poor if the FA images showed none to only second-order branch visibility, good if the third-order branch was visible, and excellent if the fourth-order branch was visible in any quadrants within the images. The visibility of the FAZ was defined as 0 (FAZ not visible) or 1 (FAZ visible with the border appreciated) (Figure 2).

In addition, the image intensity was assessed with ImageJ software (Image Jdev, Fiji contributors) in a standardized method. A total of five boxes measuring a 50- x 50-pixel distance were defined as the region of

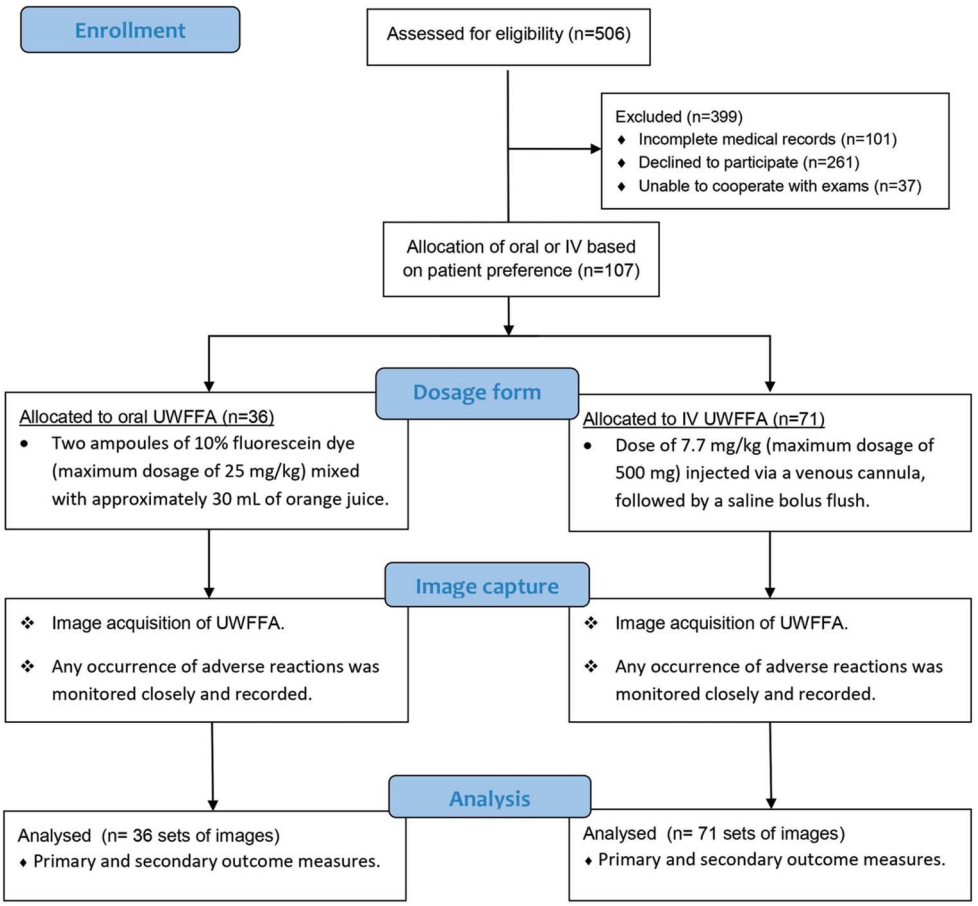

Fig. 1. Workflow and protocol of study enrollment, oral and IV UWFFA protocol and outcome analysis.

interest (ROI) on each FA image in any given set. These five boxes were constructed in a petaloid box pattern with each box at a distance of 100 pixels from the optic disk (Figure 3). An image overlay mask was applied to each of the background areas encompassing the ROIs (Figure 3; dashed box). This method effectively prevented artifacts such as eyelids or eyelash contours from affecting the subsequent intensity calculation.

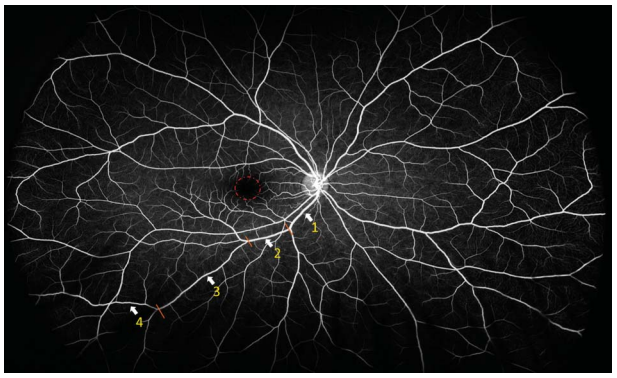

Fig. 2. Image quality based on visibility of the retinal vessel branches—0: first order branch not visible; 1: first order branch visible; 2: second order branch visible; 3: third order branch visible; and 4: fourth order branch visible (the order of the vessel branches is marked by numbers). Image quality based on visibility of the FAZ—0: FAZ not visible; 1: FAZ visible and the border appreciated (red border).

On each frame of the FA, the background fluorescence intensity was determined (sum of the grayscale intensity for each pixel within all the selected regions, divided by the total number of pixels). The background fluorescence intensity was then subtracted from the fluorescence intensity within the ROI as acquired above, resulting in a fluorescence intensity above background. The fluorescence intensity above background was subsequently summed to yield the net fluorescence above background on that particular frame of the angiogram. All values of net fluorescence above background from all frames in a patient were then averaged to yield the fluorescein intensity.

The goal was to create an image overlay mask that encompassed all lesion fluorescence with minimal inclusion of background.[12] Mean fluorescein intensities were then reported as grayscale values.

Outcome Measures

The primary outcome measure was the graded quality of the FA images based on retinal vessels

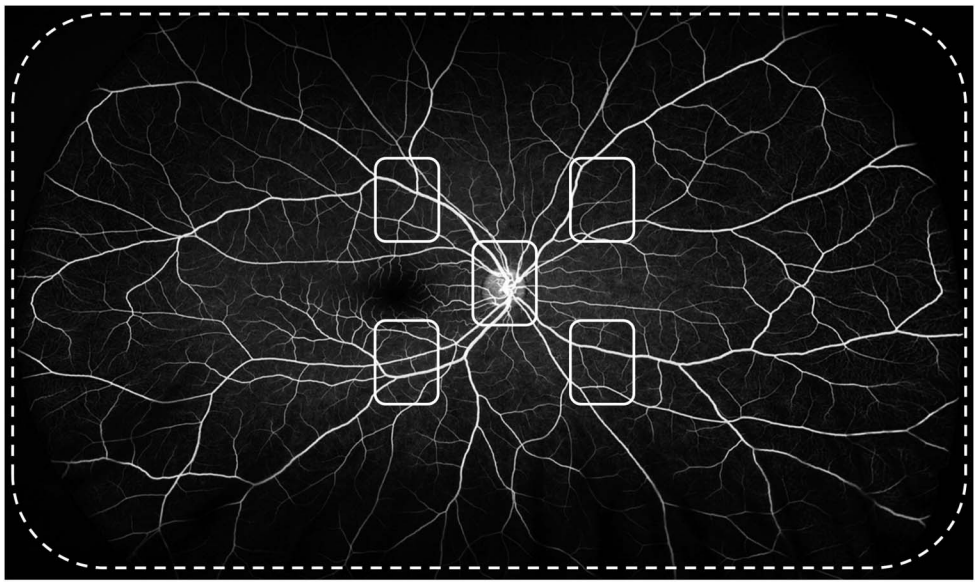

Fig. 3. Illustration of image overlays for determination of fluorescein intensity. Using ImageJ (image JDev, Fiji contributors), the ROI was defined using a petaloid box pattern each at a pixel distance of 100 from the optic disk (each white box measuring a 50 × 50 pixel distance). An image overlay mask was applied to the background area encompassing the ROIs (white dashed box). On each frame of the FA, the average background fluorescence intensity was determined (sum of the grayscale intensity for each pixel within all the selected regions divided by the total number of pixels). The average background fluorescence intensity per pixel was subtracted from the fluorescence intensity of each pixel within the ROI, and the fluorescence intensity above background for each pixel was summed to give the net fluorescence above background on that frame of the angiogram.

and FAZ visibility. The outcome was reported in the proportions of patients with the specified image quality grade. Secondary outcomes comprised the time required to reach first dye appearance and peak fluorescence, and the mean fluorescence intensity of the image sets. In addition, the incidence of adverse reactions related to the examination was investigated.

Image graders were unaware of the route and the dosage of fluorescein administration. Clinical coordinators were aware of both the drug and regimen. Patients and their parents were aware of the route of fluorescein administration.

Statistical Analysis

Univariate and multivariate analyses were performed with SPSS Version 26.0 (IBM Corp, NY). Two-sample t-tests were used to compare the age, gestational age (GA) and body weight (BW) between the oral and IV FA groups. A chi-square (χ^2) analysis was performed to compare categorical outcome measures between groups. Fisher's exact test was used to compare image quality based on retinal vessels and FAZ visibility. The Mann–Whitney *U* test was performed to compare the time taken to reach first dye appearance and peak fluorescence, and the fluorescein intensity between the groups. Normality of the distribution was assessed by review of relevant plots. If there was a non-Gaussian distribution, the median and interquartile ranges were calculated. The nonparametric Wilcoxon signed-rank test was used to test for differences among the groups in continuous variables in such cases. *P* values less than 0.01 were considered statistically significant. Multivariable logistic regression was performed to adjust for any possible effect of age, sex, BW, and GA on image quality.

Results

Study Population

Upon enrollment and review, there were comparable characteristics in both demographics and ocular characteristics among the IV and oral FA groups (Table 1). Fluorescein angiography images from a total of 107 patients (71 IV, 36 oral) were included and reviewed in the study. Both groups had greater proportions of men (64.8% in the IV group and 72.2% in the oral group). Gestational age and birthweight (BW) exhibited no significant imbalance among the groups. The mean age at which FA was performed was 7.39 ± 1.95 years for IV FA and 6.83 ± 2.12 years for oral FA.

Among patients with FA images included in this study, 14 patients (19.7%) from the IV FA group and 11 patients (30.6%) from the oral FA group were referred for ROP evaluation, but were not diagnosed with ROP. However, such patients were still enrolled for long-term follow-up with standardized FA performed. All the patients had a well-attached retina. There was no statistically significant difference in the proportions of ROP patients with different stages and zones, and proportions with plus diseases.

Comparison of Image Quality Based on Grading

Image quality was graded based on retinal vessels and FAZ visibility for all included sets of images. A

Table 1. Characteristics of Infants With ROP or Prematurity History at Enrollment

Variables	Intravenous, n = 71	Oral, n = 36	*P*
Male, n (%)	46 (64.8)	26 (72.2)	0.44
GA, weeks (mean ± SD)	27.86 ± 3.75	28.9 ± 5.01	0.62
Birthweight, grams (mean ±SD)	1055.68 ± 544.74	1242.06 ± 800.00	0.33
Age, y/o	7.39 ± 1.95	6.83 ± 2.12	0.14
Body weight, kg (mean ±SD)	24.61 ± 4.12	23.45 ± 3.57	0.15
No ROP, n (%)	14 (19.7)	11 (30.6)	0.21
Stage 1/2/3/4/5	2/4/47/3/1	0/3/22/0/0	NS
Zone I/II/III	6/46/1	4/18/3	0.13
Plus, n (%)	33 (46.4)	19 (52.8)	0.58

Statistical significance shown at $P < 0.01$.
NS, not significant.

total of 65 patients (91.5%) in the IV FA group had image sets graded as excellent compared to only 20 patients (55.6%) in the oral FA group based on retinal vessel visibility ($P < 0.01$; Figure 4). Correspondingly, six patients (16.7%) in the oral FA group exhibited poor image quality compared to one patient (1.4%) in the IV FA group ($P < 0.01$). Considering images with good or better quality in only the oral FA group, there were 30 patients (83.4%) in total [20 patients (55.6%) with excellent image quality and 10 patients (27.8%) with good image quality].

In a multivariate regression analysis, after adjusting for baseline age, BW, GA, and sex, the proportion of images graded with excellent quality was significantly greater than those with good and poor quality in the IV FA group compared with the oral FA group (Table 2; $P < 0.01$). Image quality grading based on the FAZ border revealed that all 71 patients (100%) in the IV FA group had intact visibility of the FAZ, which was significantly higher than the 28 patients (77.8%) in the oral FA group. Four patients (22.2%) in the oral FA group exhibited no visible or clear FAZ in the analyzed images.

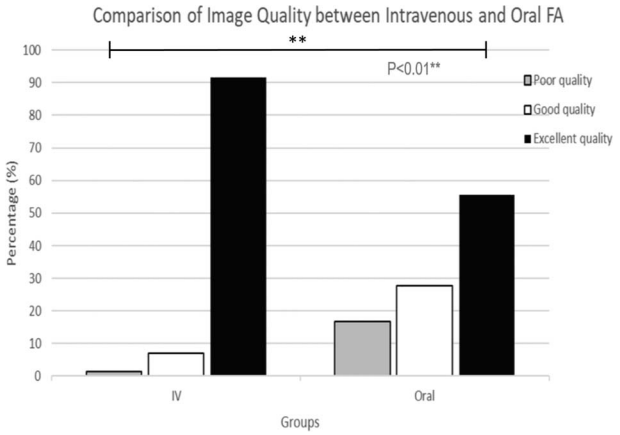

Fig. 4. Histogram of the image quality comparison between IV and oral FA.

Time to Reach First Dye Appearance, Peak Fluorescence, and Overall Peak Intensity

The average time taken to reach first dye appearance in the IV FA images was significantly shorter than that of the oral FA images (IV FA, 21.6 seconds ± 10.2 seconds; oral FA 5 minutes 11 seconds ± 2 minutes 20 seconds, $P < 0.01$; Table 3). Similarly, the median time to reach peak fluorescence within the image sets was significantly shorter in the IV FA group than in the oral FA group (IV FA, 32.1 seconds ± 13.4 seconds; oral FA 9 minutes 10 seconds ± 3 minutes 55 seconds, $P < 0.01$).

In the mean net fluorescence intensity measured in grayscales, images acquired from IV FA generally had greater fluorescence intensity than those acquired from oral FA, which was statistically significant (IV FA, 141.41 ± 29.09; oral FA 111.25 ± 45.68, $P < 0.01$). The average background intensities for the oral and IV groups were 12.67 ± 4.13 and 14.39 ± 5.98, respectively ($P = 0.12$; data not shown in Table).

Adverse Reactions

The proportions of patients who experienced adverse reactions in both the IV and oral FA groups were low, with no significant difference between them ($P = 0.22$; Table 3). In the IV FA group, only one patient (1.4%) experienced nausea or vomiting during the examination, and one patient (1.4%) exhibited itching with localized rash after the examination, and both cases resolved spontaneously before the patients were discharged. There were two patients (5.6%) with symptoms of nausea or vomiting after drinking the fluorescein solution in the oral FA group, after which the symptoms were alleviated, and the subsequent FA examination was tolerated well.

Discussion

This study examined the use of UWFFA by comparing its IV and oral forms in the clinical

Table 2. Image Quality Based on Retinal Vessel and FAZ Visibility

Variables	Intravenous, n = 71	Oral, n = 36	Remarks (*P*)
Image quality	65 (91.5)	20 (55.6)	$P < 0.01$*
Fourth-order branch visible (excellent), n (%)			
Third-order branch visible (good), n (%)	5 (7.0)	10 (27.8)	
None to only second-order branch visible (poor), n (%)	1 (1.4)	6 (16.7)	
Adjusted for age, BW, GA, gender	Image quality: Excellent versus Good & poor		MVA: $P < 0.01$*
Fovea avascular zone			
FAZ intact, n (%)	71 (100.0)	28 (77.8)	$P < 0.01$*
No visible FAZ, n (%)	0 (0.0)	4 (22.2)	

*Significance shown at $P < 0.01$.
MVA, multivariate analysis.

follow-up of pediatric patients with a history of ROP or prematurity. Using standardized fluorescein and image grading protocols, and objective image processing methods, it was shown that IV FA was more likely to achieve excellent image quality than oral FA in ROP patients followed up at school age, regardless of age, sex, GA, and BW. Despite this finding, there was still a relatively high proportion of images acquired via oral FA (83.4% and 77.8% of patients with image quality graded good or better based on peripheral retinal vessel and FAZ visibilities, respectively). This indicates that FA images acquired from oral fluorescein are still viable and useful in the clinical follow-up of ROP pediatric patients. In addition, the procedure is well tolerated in most pediatric patients. No major serious allergic reaction was reported in our study.

By showing the feasibility of oral FA in obtaining high-resolution, good-quality angiograms for long-term follow-up of ROP patients, the potential distress of children or parents regarding undergoing the procedure is reduced because no intravenous access is required. However, the results of this study suggest that a personalized examination protocol may be needed for performing oral FA to improve the cooperativity of patients and the quality of images acquired. This is because of the longer time required for achieving observable dye appearance and peak fluorescence in oral FA. Although considered safe and effective for younger children who cannot tolerate phlebotomy, oral FA would require cooperation between trained expertise and pediatric patients in view of the longer time needed to complete the examination.

In general, the overall fluorescence intensity of oral FA was shown to be less than that of IV FA in our study. However, the mean fluorescence intensity acquired with oral FA (111.25 ± 45.68) was well beyond the mean background fluorescence (12.67 ± 4.13) measured in all images using our standardized method, thus suggesting that clinicians would still be able to clearly appreciate the fluorescent details of oral FA images in daily clinical practice. Our study technique can avoid a subjective assessment of the fluorescence intensity in all the included images. This is crucial in comparisons of this kind because the image quality or analysis can be greatly affected by factors such as the degree of frame exposure, varying fluorescence with time and lesion appearance.[12,13]

Table 3. Time to First Dye Appearance and Peak Fluorescence; Fluorescein Intensity, and Adverse Side Effects

	Intravenous, n = 71	Oral, n = 36	*P*
Time to first dye appearance, (mean ± SD)	21.6 seconds ± 10.2 seconds	5 minutes 11 seconds ± 2 minutes 20 seconds	<0.01*
Time to peak fluorescence of images, (median ± IQR)	32.1 seconds ± 13.4 seconds	9 minutes 10 seconds ± 3 minutes 55 seconds	<0.01*
Fluorescein intensity, (mean ± SD)	141.41 ± 29.09	111.25 ± 45.68	<0.01*
Incidence of adverse effect:			
Nausea or vomiting, n (%)	1 (1.4)	2 (5.6)	0.22
Anaphylaxis, n (%)	0	0	N/A
Itching/Localized rash, n (%)	1 (1.4)	0	0.47

*Significance shown at $P < 0.01$.
IQR, Interquartile range.

The characteristics of the test dynamics elucidated by our study results indicated that performing an optimal oral FA examination in pediatric patients would require an imaging time of at least 10 minutes. One limitation of oral FA is its inability to clearly depict the arteriovenous phase and the progressive visualization of retinal vessels.[4] In addition, our results, which showed that four patients (22.2%) in the oral FA group had poorly delineated FAZs, were consistent with previous reports suggesting lower reliability of oral FA in FAZ evaluation.[14]

Probable adverse reactions following fluorescein sodium ingestion are related to the systemic reaction toward fluorescein sodium metabolites. Most adverse reactions to fluorescein are usually mild and self-limiting. Transient nausea and vomiting are reported to be the most common reactions of patients treated with fluorescein injection.[15] In a large-scale study, only a 0.7% incidence of nausea severe enough to interrupt the procedure was reported among 11,898 cases of fluorescein angiography.[15] The incidence of anaphylactoid shock secondary to fluorescein administration is extremely rare. Consistent with our data, the aforementioned survey of 11,898 cases of intravenous fluorescein use in retinal angiography reported no cases of severe drug-induced events.[15] The use of fluorescein in pediatric patients was also tolerable, as a study by Chee et al[16] revealed that fluorescein angiography was not associated directly with systemic adverse events in pediatric patients. When comparing oral with IV fluorescein, a study by Marziali et al[17] showed that oral fluorescein angiography had a reduced incidence of adverse events compared with intravenous fluorescein in children aged 17 and under.

Oral FA can ameliorate the challenges of obtaining IV FA images in clinical follow-up, because the latter is more difficult in pediatric patients who are intolerant of phlebotomy. There may also be a lack of availability of the expertise required to perform IV access in ophthalmology clinics. There have been varying reported protocols regarding oral fluorescein ingestion based on different imaging modalities and groups in the literature.[10,18,19] Moreover, our study is the first to adopt a standardized methodology in objective comparisons of the image quality and test dynamics between oral and IV FA in a large cohort of ROP pediatric patients. It is worth noting that based on these results, subsequent studies on the diagnostic value or utility of oral FA regarding long-term findings of ROP patients can be performed.

The limitations of our study include its retrospective nature and the lack of randomization between groups. However, there was a comparative baseline in sex, age, BW, and ROP profile between the oral and IV FA groups. Adjustment for possible confounders in the image quality comparison revealed consistent conclusions, thus showing the robustness of the results. There was concern about possible statistical pitfalls in view of the unequal numbers between the two groups. This was addressed using nonparametric tests, whereby nonnormal distribution was assumed, and the underlying foundation of the Kruskal–Wallis test statistics stipulates that each group can have a different number of observations.[20]

Acquired images may be affected by tolerability and cooperation of young patients. Variations in the bioavailability of fluorescein may also influence the intensity of images in all FA phases. Therefore, we adopted standardized protocols for image intensity analysis as reported above, which focused on net fluorescein intensity subtracting the background values, thus striving for objectivity in the analysis. One of the disadvantages of oral FA is its off-label usage in many health care systems today. Thus, new studies involving the use of oral FA are ever more essential to provide more evidence that oral FA can be safely and effectively applied for clinical purposes.

Conclusion

In conclusion, UWFFA provides excellent image quality of both the peripheral retina and macula in the ROP pediatric population during clinical follow-up. Although a significantly higher proportion of IV FA images had better quality than oral FA images, there remained a large proportion of patients with oral FA images (83.4%) that exhibited good or excellent image quality in retinal vessel visibility. Therefore, oral FA is still an effective and useful alternative to the IV route in the long-term evaluation of ROP pediatric patients.

Key words: ultrawide-field fluorescein angiography, oral fluorescein, intravenous fluorescein, retinopathy of prematurity.

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The study design, data analysis or interpretation, and writing were all completed independently by all the authors.

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