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BRIEF COMMUNICATION

# A prospective evaluation of adverse events occurring in children undergoing fundus fluorescein and indocyanine green angiography

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## INTRODUCTION

Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) are the gold standard tests to detect posterior segment inflammatory involvement. Adverse events (AEs) reported with FFA range from mild, including nausea, vomiting, extravasation, sneezing, pruritus; to moderate, namely rash/urticaria, syncope/dizziness/hypotension, angioedema, dyspnoea; to severe, including anaphylaxis/bronchospasm, myocardial infarction and seizure [1, 2]. ICGA is rarely associated with nausea and vomiting, more commonly with urticarial/hives, hypotension and vasovagal reaction/syncope [1, 2]. Based on these findings, the use of FFA/ICGA in children and young people (CYP) has been limited by safety concerns. Although reports indicate the safety of angiographic procedures in CYP (Table 1), further evidence is required to confirm it, as larger numbers are needed to explore rare events. In addition, similar information regarding ICGA in CYP is needed. Here we report our experience with AEs associated with angiographic procedures in CYP.

## METHODS

Prospective evaluation of CYP age 5–17 years undergoing outpatient oral or intravenous (IV) FFA and/or ICGA without general anaesthesia between January 2015 and December 2017 at Moorfields Eye Hospital, London, UK (Trust Service Evaluation CA15/ONSP/23). All patients signed a consent form. Electronic medical records were prospectively compiled to identify AEs within 24 h from the procedure with an observation of 60 min. Data recorded included demographics and clinical indications.

The protocol for performing FFA/ICGA in CYP is included as Supplementary information.

## RESULTS

One hundred and fourteen consecutive CYP were included (median age 11.5 years; 55 (48.2%) female, 59 (51.8%) male). Eighty-two (71.9%) received IV fluorescein, 10 (8.8%) oral fluorescein and 22 (19.3%) ICGA. Most common clinical indications include uveitis (43.0%), with intermediate and posterior uveitis accounting for 13.1% and 12.3%, respectively; Coats disease (12.3%), familiar exudative vitreoretinopathy (8.9%), unknown macular lesions (7.9%), incontinentia pigmenti (4.4%) and abnormal retinal vessels (3.5%). During/after IV FFA, 26 (31.7%) CYP experienced one or more AEs. In 25 (96.1%), AEs were mild, including nausea, vomiting, itchy skin, hot flush and extravasation. One patient (3.8%) had bronchial spasm as a severe adverse reaction. Following oral FFA, 1 patient (10%) had vomiting. Following ICGA, 1 patient (4.5%) developed itchy skin and hot flushes. AEs are described in Table 2.

## DISCUSSION

Our study showed that mild AEs can happen after FFA and ICGA, and they appear to be more common after IV FFA compared to oral FFA (31.7% vs 10%, respectively). These findings are in contradiction to previous publications which reported no AEs after FFA/ICGA (Table 1). Although AEs appear less common after oral administration of fluorescein compared to IV, data cannot be compared given the different sizes of the samples (also the lack of serious AEs after ICGA is likely due to the small number of the sample). However, the authors believe that, considering the inferior angiographic details, oral administration cannot be considered the route of choice [3].

Strengths of this study include the inclusion of consecutive patients and the relatively large sample size, allowing detection of serious AEs to be added to the existing paediatric literature. However, the sample size is not large enough to inform practice.

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**Table 1.** Studies reporting adverse effects following fluorescein and/or indocyanine angiography in paediatric population by year and performed procedure.

| Reference | Study design | Origin | Sample size | Age (years) | Procedure | Clinical indication | Adverse effects |
|---|---|---|---|---|---|---|---|
| Chee 2020 | Single-institution retrospective chart review | USA | 115 | Average age inpatients 2.52, outpatients 10.7 | IV FFA (65 inpatients under GA, 60 outpatients) | Inpatients: ROP (44.6%), Coats disease (6.2%), FEVR (6.2%). Outpatients: FEVR (15.0%), Coats disease (20.0%), sickle cell retinopathy (8.3%), retinopathy of prematurity (3.3%) | No significant adverse events were associated directly with FFA |
| Temkar 2019 | Retrospective chart review | India | 22 | Age ranged from 4 weeks to 10 years | IV FFA under paediatrician monitoring (in babies <3 months) or under general anaesthesia (in bigger children) | Retinal vascular disease, including coats disease, FEVR, ROP, congenital retinal folds, double optic nerve head, persistent foetal vasculature and incontinentia pigmenti | No allergic reactions to fluorescein injection like rash, respiratory distress, tachycardia, fever and local injection site reactions |
| Abraham 2019 | Retrospective chart review | USA | 14 | 11 years (range 7–16 years) | IV FFA under GA (apart from select older patients—13 years of age and older) | Uveitis, six patients (43%) demonstrated intermediate uveitis, and 8 patients (57%) demonstrated panuveitis | No adverse reactions to the fluorescein dye solution |
| Ali 2018 | Case series | UAE | 18 | Age 4–16 years | Oral FFA | 12 cases of posterior uveitis or panuveitis and 6 cases of Coats disease, FEVR thalassaemia, TINU | There were no adverse effects during or after the procedure |
| Azad 2008 | Case series | India | 20 | – | IV FFA under GA | ROP | No adverse reactions to the fluorescein dye solution |
| Kinsella 1988 | Case report | Ireland | 1 | 16 | Oral FFA | Optic disc oedema | Sweats nausea and dizziness, blood pressure 85/30 mmHg—history of atopic eczema |
| Nayak 1987 | Case series | India | 28 | Ages 1 month to 10 years | Oral FFA | No detectable fundus lesions, pseudopapilloedema | No major complications or any allergic reactions were observed |
| Shafy 2020 | Retrospective chart review | USA | 100 | Median age of 12 years (9.5 ± 7.4 years) | ICGA under GA | To study vascular supply of various tissue beds | No adverse respiratory or hemodynamic events |
| Patel 2017 | Prospective observational case series | UK | – | Infants | ICGA under GA | ROP | Intravenous ICGA was well tolerated in all cases with no early adverse side effects. |
| Diallo 2009 | Prospective, nonrandomized observational study | Burkina Faso/ India | 26 | Average age 14.3 years (range, 9–24 years) | ICGA | Sickle cell disease | No adverse reactions to the dye solution |

*FFA* fundus fluorescein angiography, *IV* intravenous, *GA* general anaesthesia, *ICGA* indocyanine green angiography, *ROP* retinopathy of prematurity, *FEVR* familial exudative vitreoretinopathy, *TINU* tubulointerstitial nephritis and uveitis syndrome.

**Table 2.** Adverse events following angiographic procedures.

| Adverse events | Nausea | Vomiting | N&V | Itchy skin | Hot flush | Bronchial spasm | Extravasation | Total AE | No AE |
|---|---|---|---|---|---|---|---|---|---|
| IV FFA | 16 (19.51%) | 9 (10.97) | 6 (7.3%) | 2 (2.44%) | 2 (2.44%) | 1 (3.8%) | 1 (3.8%) | 26/82 (31.71%) | 56 (68.29%) |
| Oral FFA | | 1 (10.00%) | | | | | | 1/10 (10.00%) | 9 (90.00%) |
| IV ICG | | | | 1[a] (4.54%) | 1[a] (4.54%) | | | 1/22 (4.54%) | 21 (95.46%) |

Adverse events were categorised as per Food and Drug Administration as mild if transient, not requiring any intervention and characterised by rapid and complete resolution with no sequelae; moderate if transient, but requiring some form of medical treatment, characterised by complete and gradual resolution with no sequelae or threat to patient's safety; severe if exhibiting prolonged effects requiring intense treatment and posing a threat to patient's safety.

The sum of the single reactions is higher than total AEs—37 reactions in 82 patients—since a group of 6 patients had in total 17 reactions; [a]two reactions in the same patient.

*N&V* nausea and vomiting, *AE* adverse event, *total AE* number of patients who experienced one or more reactions.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41433-022-01951-5.

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