

A Prospective Observational Study on the Risk of Contrast-Induced Nephropathy Among Patients Undergoing Fundus Fluorescein Angiography

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ABSTRACT

Objective: To determine the incidence of contrast-induced nephropathy (CIN) among patients undergoing fundus fluorescein angiography (FFA)

Methods: One hundred fifty-nine (159) patients from the Ophthalmology out-patient department were enrolled in this prospective, observational study. Serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) were measured within 7 days before and 48 to 72 hours after FFA. Subjects were stratified into low-, intermediate-, and high-risk groups for developing CIN according to baseline eGFR. CIN was defined by an increase in SCr by more than 25% or by 0.5 mg/dL within 72 hours of intravascular administration of contrast media. The incidence of CIN, changes in SCr levels, and changes in eGFR were analyzed.

Results: Of the 144 subjects who completed the study, 106 (73.6%) were females, 105 (72.9 %) were diabetics, and 57 (39.6%) had elevated baseline SCr. Four (4 or 2.8%) patients developed CIN after FFA, all of whom had normal baseline SCr and were stratified as low-risks. Overall, there were no significant changes in the means of SCr (1.18 ± 0.56 vs 1.16 ± 0.52 , $p = 0.13$) and eGFR (64.53 ± 26.05 vs 64.94 ± 24.88 , $p = 0.64$) before and after FFA. In the low-risk group, the means of SCr and eGFR remained unchanged after FFA ($p = 0.06$ and $p = 0.15$, respectively). In the intermediate-risk group, no significant change was appreciated in SCr levels ($p = 0.07$) however a significant improvement in eGFR ($p = 0.006$) was seen. Interestingly, a significant decrease in SCr levels ($p = 0.004$) as well as a significant improvement in eGFR ($p = 0.02$) was noted after FFA in the high-risk group.

Conclusion: The incidence of CIN among patients undergoing FFA in our cohort was 2.8%. There was no prolonged or serious worsening of renal function based on SCr and eGFR before and after FFA overall, and among low-, moderate-, and high-risk groups.

Keywords: fluorescein angiography, contrast-induced nephropathy, acute kidney injury, incidence, contrast media, creatinine, estimated glomerular filtration rate.

Fundus fluorescein angiography (FFA) has been widely used since the 1960s for the evaluation of a wide array of retinal disorders. The contrast media used in this procedure is sodium fluorescein, a non-iodinated, orange-red crystalline hydrocarbon ($C_{20}H_{12}O_5Na$) with an osmolality of 572 - 858 mOsm/kg, which readily diffuses through most body fluids.¹ The normal adult dose is 500 mg (100 mg/mL) via intravenous administration. It is primarily metabolized by the kidneys and is completely excreted through urine within 48 to 72 hours of administration.¹

Contrast-induced nephropathy (CIN) is a form of acute kidney injury (AKI) defined as an elevation of serum creatinine ($\geq 25\%$ or 0.5 mg/dL) within 72 hours of intravascular administration of contrast media in the absence of an alternative etiology.² A large number of studies have demonstrated the toxic effects of iodinated contrast media on the kidneys.³⁻⁴ Iodinated contrast media causes renal vasoconstriction which leads to decreased renal blood flow, accumulation of contrast media, and direct cellular toxicity to renal structures.³⁻⁴ Risk factors for CIN from iodinated contrast media include older age, elevated serum creatinine (SCr), dehydration, pre-existing renal disease, heart failure, higher volumes of injected contrast media, intra-arterial route of administration, and concurrent intake of nephrotoxic drugs.³⁻⁴

Unlike other iodinated contrast media, little is known on the effect of sodium fluorescein on the kidneys. There are currently no guidelines in the ophthalmology community on when to require measurement of renal function or who needs referral to a nephrologist for clearance prior to FFA. Common practice dictates the avoidance of FFA in patients with renal insufficiency based on published data showing nephrotoxic effects of iodinated contrast media.³⁻⁴ There is, however, inadequate data on CIN from FFA. As of this writing, only 4 published studies, with sample sizes ranging from 44 to 160, on the effect of FFA on renal function are known to the authors.⁵⁻⁸ Using SCr and estimated glomerular filtration rate (eGFR) as markers of renal function, 3

studies showed no significant effect of FFA on renal function.⁵⁻⁷ On the other hand, Alemzadeh-Ansari *et al.* noted elevation of SCr in 9 out of 44 (20%) of diabetic patients after FFA.⁸ The authors, however, did not specify if this increase in SCr was significant or not. Limited studies with conflicting results necessitate the need for a prospective study with a large cohort of patients to validate their findings.

METHODS

Consecutive patients aged 18 years and above that required FFA at the Ophthalmology out-patient department were enrolled in the study. Patients were excluded if they (1) underwent a procedure using contrast media within 2 weeks from study entry, (2) were using nephrotoxic drugs such as non-steroidal anti-inflammatory drugs, corticosteroids, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers within 2 weeks from study entry, or (3) were pregnant or lactating.

Sample size was calculated based on the incidence of CIN among patients undergoing FFA assumed to be 3.2%⁶⁻⁸, with a maximum allowable error of 2% and reliability of 80%. The computed sample size was 129 subjects.

After fulfilling the eligibility criteria, informed consent was obtained from the subjects. For each subject, serum samples for creatinine determination and complete blood count (CBC) were collected within 7 days before the scheduled fluorescein angiogram. Subjects with elevated baseline SCr levels were referred to the Nephrology service for clearance prior to FFA. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula:

$$eGFR = 141 \times \min\left(\frac{SCr}{K}, 1\right)^0 \times \max\left(\frac{SCr}{K}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

where SCr is serum creatinine
K is 0.7 for females and 0.9 for males

° is -0.329 for females and -0.411 for males
min is minimum of SCr/K or 1
max is maximum of SCr/K or 1

Enrolled subjects were classified according to baseline eGFR levels into low (eGFR \geq 60 mL/min), intermediate (eGFR 30 - 59 mL/min), and high-risk (eGFR \leq 29 mL/min) for developing CIN. We used eGFR in the stratification of our subjects for the risk of developing CIN because this renal marker, unlike SCr, accounts for other factors such as age, gender, and race. The authors used the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the classification of chronic kidney disease in the categorization of subjects into low, intermediate, and high-risk groups.³

The following baseline characteristics were collected prior to FFA: (1) age, (2) sex, (3) race, (4) weight, (5) height, (6) body mass index (BMI), (7) blood pressure, (8) ocular diagnosis, (9) presence of systemic co-morbidities, (10) presence of anemia, and (10) serum creatinine.

Patient preparation prior to FFA included an (1) intradermal skin test to detect potential allergy to sodium fluorescein and (2) dilation of the pupils using 0.5% tropicamide + 0.5% phenylephrine (Sanmyd-P®, Santen Philippines Inc., Metro Manila, Philippines) ophthalmic solution. Skin tests were evaluated 30 minutes following intradermal injection. Fluorescein angiography was deferred for subjects with a positive skin test, systolic BP of \geq 160 mmHg or diastolic BP of \geq 100 mmHg. All subjects for FFA received 5 mL of 500 mg sodium fluorescein (Alcon Laboratories, Fort Worth, Texas, USA) intravenously using a 25-gauge winged infusion set via a peripheral vein in 4 to 6 seconds followed by retinal photography using the Zeiss Visucam®NM/FA or Zeiss Visupac (Carl Zeiss Meditec AG, Germany) fundus cameras. After the FFA procedure, subjects were monitored for 30 minutes for adverse reactions. If an adverse event was noted, routine care according to existing guidelines was given to the subject. Serum creatinine and eGFR measurements were repeated 48 to 72 hours after FFA for each subject. Subjects who developed CIN after FFA were immediately referred to the Nephrology service for further evaluation and management.

Statistical analysis was performed using SPSS version 10. Numerical data were expressed as means and standard deviations (SDs). Categorical variables were expressed as frequency (n) and percentage (%).

Incidence of CIN was determined by the total number of CIN cases divided by the total number of subjects who underwent FFA. Paired student's t-test was used to compare SCr and eGFR before and after FFA for all subjects and among low, intermediate, and high-risk groups. Level of significance was set at $\alpha = 0.05$.

The hospitals' Institutional Scientific Review Committee and Institutional Ethics Review Committee approved the research protocol, informed consent forms, and data collection forms prior to the commencement of this study.

RESULTS

A total of 159 subjects were enrolled from September 1, 2018 to August 31, 2019. However, only 144 patients were able to complete the study. FFA was deferred in 1 patient due to elevated blood pressure and in 3 patients who developed a positive reaction from the intradermal skin test prior to FFA. Ten (10) subjects were lost to follow-up.

The baseline characteristics of the subjects included in the study are shown in Table 1. Of the 144 subjects who completed the study, majority were females (73.6%) and were diabetics (72.9%). Mean patient age was 61 years old (range: 19 to 88). Subjects who were already diagnosed with chronic kidney disease (CKD) comprised 11.8% of the study population. The most frequent ocular diagnoses were non-proliferative diabetic retinopathy (26.4%), proliferative diabetic retinopathy (25.0%), and age-related macular degeneration (13.2%). According to baseline eGFR levels, 57.6%, 32.6%, and 9.7% were classified into low-, intermediate-, and high-risk groups respectively. Fifty-seven (57 or 39.6%) patients who completed the study had elevated SCr at baseline.

Four (4 or 2.8%) patients, all with normal baseline SCr and were stratified as low-risks, developed CIN after FFA (Table 2). Three (3) out of the 4 patients were diabetic and 2 were hypertensive. Two (2) patients experienced nausea and vomiting after undergoing the FFA procedure. All 4 subjects were advised to increase oral fluid intake and underwent repeat SCr determination after 7 days. Repeat SCr for all 4 patients who developed CIN went back to normal levels and no other treatment was given apart from oral hydration. No patient needed hospitalization or dialysis.

Table 1. Baseline Characteristics of Patients Undergoing Fundus Fluorescein Angiography (FFA)

Variables	Low-risk N=83	Intermediate- risk N=47	High-risk N=14	Total N=244
Sex				
Male, n (%)	23 (16.0)	12 (8.3)	3 (2.1)	38 (26.4)
Female, n (%)	60 (41.7)	35 (24.3)	11 (7.6)	106 (73.6)
Mean Age (years)	57	67	62	61
Mean BMI (kg/m ²)	25	24	25	24.84
Mean Baseline serum creatinine (mg/dL)	0.86	1.37	2.50	1.18
Mean Baseline eGFR (mL/min/1.73 m ²)	82.93	44.57	22.46	64.53
FFA Diagnosis				
Non-Proliferative Diabetic Retinopathy, n (%)	17 (11.8)	17 (11.8)	4 (2.8)	38 (26.4)
Proliferative Diabetic Retinopathy, n (%)	17 (11.8)	11 (7.6)	8 (5.6)	36 (25.0)
Hypertensive Retinopathy, n (%)	7 (4.9)	5 (3.5)	0 (0.0)	12 (8.3)
Age-Related Macular Degeneration, n (%)	15 (10.4)	3 (2.1)	1 (0.7)	19 (13.2)
Retinal Vein Occlusion, n (%)	3 (2.1)	2 (1.4)	1 (0.7)	6 (4.2)
Normal FA, n (%)	9 (6.3)	3 (2.1)	0 (0.0)	12 (8.3)
Other	15 (10.4)	5 (3.5)	0 (0.0)	21 (14.6)
Systemic Co-morbidities				
Hypertension, n (%)	45 (31.3)	36 (25.0)	13 (9.0)	94 (65.3)
Diabetes mellitus, n (%)	54 (37.5)	38 (26.4)	13 (9.0)	105 (72.9)
Chronic kidney disease, n (%)	0 (0.0)	4 (2.8)	13 (9.0)	17 (11.8)
Congestive heart failure, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)

Table 2. Patient Characteristics and Serum Creatinine (SCr) Levels of Subjects Who Developed Contrast-Induced Nephropathy (CIN)

Patient #	Co-morbidities	Risk-Stratification	Baseline SCr (mg/dL)	Post-FA SCr (mg/dL)	Repeat SCr (mg/dL)
Patient 1	DM, HTN	Low-risk	1.08	1.36 ↑	1.08
Patient 2	None	Low-risk	0.86	1.15 ↑	1.00
Patient 3	DM	Low-risk	1.1	1.39 ↑	0.96
Patient 4	DM, HTN	Low-risk	0.83	1.52 ↑	1.02

DM: Diabetes mellitus

HTN: Hypertension

Overall, there was no significant change in SCr (1.18 ± 0.56 vs 1.16 ± 0.52 , $p = 0.13$) before and after FFA (Table 3). When subjects were grouped according to their baseline eGFR levels, serum creatinine in the low-risk (0.86 ± 0.15 vs 0.89 ± 0.19 , $p = 0.06$) and intermediate-risk (1.37 ± 0.28 vs 1.33 ± 0.35 , $p = 0.07$) groups showed no significant changes before and after FFA. However, in subjects classified as high-risk, a statistically significant ($p = 0.004$) decrease was noted (2.50 ± 0.61 vs 2.23 ± 0.69) after FFA.

Table 3. Changes in serum creatinine (SCr [mg/dL]) and estimated glomerular filtration rate (eGFR [mL/min/1.73 m²]) after fundus fluorescein angiography (FFA) among low, intermediate, and high-risk groups

	n	Before FA	After FA	p-value
Serum creatinine				
Overall	144	1.18 ± 0.56	1.16 ± 0.52	0.13
Low-risk group	83	0.86 ± 0.15	0.89 ± 0.19	0.06
Intermediate-risk group	47	1.37 ± 0.28	1.33 ± 0.35	0.07
High-risk group	14	2.50 ± 0.61	2.23 ± 0.69	0.004
Estimated glomerular filtration rate				
Overall	144	64.53 ± 26.05	64.94 ± 24.88	0.64
Low-risk group	83	82.93 ± 16.26	81.01 ± 17.45	0.15
Intermediate-risk group	47	44.57 ± 8.60	47.77 ± 12.35	0.006
High-risk group	14	22.46 ± 5.09	27.32 ± 10.36	0.02

We also looked at the change in SCr among subjects who presented with normal SCr and those who presented with elevated SCr at baseline. The SCr values among subjects that presented with normal SCr at baseline showed no significant change (0.87 ± 0.15 vs 0.89 ± 0.18 , $p = 0.10$) after

FFA (Table 4). However, subjects who presented with elevated SCr at baseline actually showed a significant decrease (1.67 ± 0.61 vs 1.57 ± 0.59 , $p = 0.002$) in SCr levels after FFA.

Table 4. Changes in serum creatinine (SCr [mg/dL]) after fundus fluorescein angiography (FFA) among normal and elevated baseline SCr groups

	n	Before FA	After FA	p-value
Normal baseline SCr group	87	0.87 ± 0.15	0.89 ± 0.18	0.10
Elevated baseline SCr group	57	1.67 ± 0.61	1.57 ± 0.59	0.002

No significant change was also observed in eGFR (64.53 ± 26.05 vs 64.94 ± 24.88 , $p = 0.64$) before and after FFA overall (Table 3). When broken down according to risk-stratification, subjects classified in the low-risk group showed no significant change in eGFR (82.93 ± 16.26 vs 81.01 ± 17.45 , $p = 0.15$) after FFA. However, subjects in the intermediate-risk (44.57 ± 8.60 vs 47.77 ± 12.35 , $p = 0.006$) and high-risk (22.46 ± 5.09 vs 27.32 ± 10.36 , $p = 0.02$) groups showed improved eGFR after FFA.

No serious adverse events were noted in the study. Thirteen (13 or 9.0%) patients noted nausea, 8 (5.6%) had pruritus, and 3 (2.1%) experienced vomiting after FFA (Table 5). All subjects were managed accordingly and were sent home on the same day.

Table 5. Adverse events following fundus fluorescein angiography (FFA)

Side Effect/ Adverse Event	Low-risk n (%)	Intermediate-risk n (%)	High-risk n (%)	TOTAL n (%)
Nausea	9 (6.3)	4 (2.8)	0 (0.0)	13 (9.0)
Vomiting	2 (1.4)	1 (0.7)	0 (0.0)	3 (2.1)
Hives and itching	5 (3.5)	2 (1.4)	1 (0.7)	8 (5.6)
Contrast- Induced Nephropathy	4 (2.8)	0 (0.0)	0 (0.0)	4 (2.8)

DISCUSSION

The incidence of CIN following FFA in this study (2.8%) was slightly higher compared to the retrospective studies of Lee et al. (1.3%)⁶ and Almalki et al. (1%).⁷ Differences in baseline characteristics of the study populations and methodologies used such as the concentration

of sodium fluorescein may account for the slight difference in incidence of CIN from these studies. The mean age of the subjects in our study was 61 years compared to 52 years and 56 years in the studies of Lee et al. and Almalki et al. respectively.⁶⁻⁷ Some studies have identified advanced age as an independent risk factor for CIN following coronary angiography.²³⁻²⁴ Higher age is associated with deterioration of renal function leading to greater risk for CIN. Our study population also predominantly consisted of diabetics (72.9%) while that of Lee et al. only had 47.5% of their subjects who were diabetics.⁶ Although there is no conclusive evidence that the presence of diabetes mellitus (DM) with normal renal function is associated with CIN, several studies have identified DM as an independent risk factor for CIN.^{23,25-26} The presence of DM alone may predispose an individual to higher risk for CIN may be due to early renal deterioration from DM nephropathy that is not yet detected by serum creatinine. On the other hand, while all of Almalkis' subjects were diabetics, they only used half of the recommended concentration of sodium fluorescein.

Compared to the rates of CIN in contrast-enhanced CT scan (3.2 - 11%)⁹⁻¹⁵ and coronary angiography (5.1 - 29%)¹⁶⁻²¹, our CIN rate (2.8%) was considerably lower. The pathophysiology of CIN is brought about by acute renal vasoconstriction caused by the release of adenosine and endothelin²². These renal vasoconstrictors are triggered by iodinated contrast media. Renal vasoconstriction causes decrease in renal blood flow which consequently leads to stasis of contrast media in the kidneys which allows for direct cellular injury.²² However, unlike the contrast media used in coronary angiography and contrast-enhanced CT scan (CECT), fluorescein angiography uses sodium fluorescein, a non-iodinated contrast media. There is currently no evidence in literature which show that non-iodinated contrast media generates the same renal vasoconstrictors that cause acute kidney injury. Another possible explanation for the difference in CIN incidence between FFA and CECT and coronary angiography is the volume of contrast media used. In FFA, only 5 mL of 10% sodium fluorescein is used compared with higher volumes of contrast media in CECT (80 - 120 mL)¹² and coronary angiography (150 - 250 mL)²¹.

Of the 4 subjects who developed CIN after FFA, all had normal baseline SCr and all were stratified as low-risk. There were no patients in the intermediate- and high-risk groups who developed CIN. Since

the subjects in the study were aware of their risk-stratifications prior to the procedure, those classified in the intermediate- and high-risk groups probably had a more concerted effort to hydrate themselves days before and after FFA. This may explain why none of the subjects in the intermediate- and high-risk groups developed CIN.

Two of the 3 subjects who had vomiting after FFA eventually developed CIN. Vomiting is a known side-effect of the procedure but it usually occurs in a very small proportion (0.3 - 0.4%) of patients. This side effect may have caused significant gastrointestinal losses and subsequent dehydration of subjects that led to increase in SCr. This study, however, is not powered to determine if the occurrence of vomiting is truly an independent risk factor for the development of CIN.

There was no significant worsening of acute renal function based on SCr and eGFR after FFA. The results support the findings of Kameda et al., Lee et al., and Almalki et al. who also used SCr and eGFR to assess renal function before and after FFA.⁵⁻⁷ An unexpected outcome was that SCr and eGFR levels actually significantly improved after FFA in the high-risk. A similar finding was seen by Lee et al. who classified subjects as high-risk based on their baseline SCr (>2.0 mg/dL).⁶ As mentioned earlier, a plausible explanation to this is that patients at higher risks may have a conscious effort to hydrate themselves more compared with patients with lower risk.

The limitation of this study is that it is not powered to identify which factors are associated with CIN from FFA. Based on our results, baseline serum creatinine may not be a good predictor of the development of CIN post-FFA since all 4 subjects who developed CIN in this study presented with normal SCr at baseline. Further studies with a larger cohort of subjects to address this issue are recommended.

CONCLUSION

The incidence of contrast-induced nephropathy among patients undergoing fundus fluorescein angiography in our cohort is 2.8%. All subjects who developed CIN exhibited normal serum creatinine levels within 7 days without the need for hospitalization or dialysis. Prolonged or serious worsening of

renal function, as measured by serum creatinine and estimated glomerular filtration rate before and after fundus fluorescein angiography, was not noted in all subjects in our study, including those classified as intermediate- and high-risk for developing contrast-induced nephropathy.

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