Slow versus Rapid Fluorescein Injection in Angiographic Studies for Retinal Vascular Disorders

Hassan Behboudi, MD; Arash Pourhabibi, MD; Abtin Heidarzade, MD; Azadeh Haghbin, MD

Guilan University of Medical Sciences, Rasht, Iran

Purpose: To compare the incidence of adverse reactions following rapid versus slow fluorescein injection for fundus angiography.

Methods: This randomized controlled trial was performed on 500 patients with retinal vascular disorders. Subjects with central serous retinopathy, age-related macular degeneration and retinal pigment epithelial changes were excluded. Pregnancy, asthma, allergic diseases and previous history of reactions to fluorescein were other exclusion criteria. Patients were randomly divided into two equal groups who received slow infusion of dye (over 15-25 seconds) versus the usual rapid injection (in 5-8 seconds), and were compared for adverse effects.

Results: Overall, 47 (9.4%) patients including 34 (13.6%) subjects in the rapid group and 13 (5.2%) cases in the slow group developed adverse reactions (P=0.001, relative risk=2.6). All adverse reactions were categorized as mild; no instance of moderate or severe reactions was observed. There was a lower incidence of nausea and vomiting with slow infusion of fluorescein (P=0.02), however no statistically significant difference was observed in the frequency of vertigo and vasovagal reactions between the study groups.

Conclusion: Slow fluorescein injection during fundus angiography, instead of the usual rapid application, can be an effective way to reduce the incidence of nausea and vomiting in patients whose first phase of angiography is of little diagnostic importance.

Key words: Fluorescein Angiography; Nausea; Vomiting; Slow Infusion

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Correspondence to: Hassan Behboudi, MD. Associate Professor of Ophthalmology; Department of Ophthalmology, Amiralmomenin Hospital, 17 Sharivar St., Rasht, Guilan, Iran; Tel: +98 131 2238306, Fax: +98 131 2227409; e-mail: behboudi_dr@yahoo.com

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INTRODUCTION

Fluorescein angiography (FAG) is a diagnostic technique used for interpretation of pathologic ocular states. It allows sequential visualization of blood flow simultaneously through retinal, choroidal and iris tissues.[1] In wide use for over 40 years, it has become a valuable tool in evaluation, understanding and treatment of ocular diseases.[1,2]

Although considered a relatively safe procedure, numerous adverse reactions have been reported in the literature which may be divided into mild (nausea, vomiting, pruritus, sneezing, vasovagal disorders), moderate (urticaria, other skin eruptions, syncope, thrombophlebitis, pyrexia, local tissue necrosis, muscular paralysis), and severe (bronchospasm, laryngeal edema, circulatory shock, myocardial infarction, tonic-clonic seizures).[3-5] Previous studies indicate

that most adverse reactions are mild (in 2% to 14% of cases); moderate and severe reactions are infrequent (<1%).[3,4]

The exact mechanism of adverse reactions in FAG is not clearly understood. Proposed mechanisms include: histamine release of non-allergic nature in the absence of antigen-antibody reactions (anaphylactoid reactions); immediate hypersensitivity (anaphylactic reactions); a vasovagal phenomenon resulting in bradycardia, arterial hypotension and reduced cardiovascular perfusion; anxiety-related medullary sympathetic discharge eliciting tachycardia and myocardial stress; direct vasospastic effect of intravenous injection; drug manufacturing contaminations; systemic effect of topical mydriatics, particularly phenylephrine; or any combination of the above mentioned factors.[5]

Common conditions for which FAG is routinely used include diabetic retinopathy, choroidal neovascularization, cystoid macular edema, central serous chorioretinopathy and venous occlusive diseases.[6] The reported frequency of adverse reactions following FAG varies and most related studies are retrospective in nature. The purpose of the current study was to compare the incidence of adverse reactions following rapid versus slow injection of fluorescein during fundus angiography.

METHODS

This single-blind, randomized, controlled trial was performed on 500 patients suffering from diabetic retinopathy, hypertensive retinopathy or retinal vascular disorders (arterial and venous occlusive diseases). The study was approved by the local ethics committee and informed consent was obtained from all patients. Subjects with central serous retinopathy, age-related macular degeneration, retinal pigment epithelial changes and cystoid macular edema were excluded. Prior history of reaction to fluorescein, asthma, allergic disease and pregnancy were other exclusion criteria.

Pupils were dilated at least 5 to 6 mm with cycloplegic drops (cyclopentolate 5% and tropicamide 0.5% one drop every 5 minutes repeated four times). Patients were trained for the procedure to improve their cooperation during angiography and the technician assisted the patient during the procedure to minimize anxiety and discomfort. Before injection of fluorescein, a red-free image was taken from each fundus. Sodium fluorescein 10% was used in a single 5 ml dose, injected into the cubital vein, with manual infusion speed of approximately 0.2 ml per second in the slow group (over 15-25 seconds), and approximately 1 ml per second in the rapid group (in 5-8 seconds). Images (approximately 6 depending on the patients' condition) were taken at appropriate intervals using a Topcon Retinal Camera 50 FX.

Patients were under close observation in the eye clinic for at least 15 minutes after angiography. Twenty-four hours after discharge from the clinic, all patients were contacted by telephone and interviewed about events within this period. Reactions which occurred up to 24 hours after the procedure were considered to be related to the test. Adverse reactions to fluorescein were defined based on the work by Yannuzzi et al.[5] Local dye leakage was not considered as an adverse reaction. Relative risk (RR) and 95% confidence intervals (CI) were calculated for categorical variables; Chi-square and *t* tests were used for comparing frequency and mean values, respectively. Significance level was set at $P<0.05$.

RESULTS

This randomized trial was conducted on 500 patients including 232 (46.4%) male and 268 (53.6%) female subjects with mean age of 55.7±14.5 (range, 38-69) years. There was no significant difference in age between the slow (55.8±13.8 years) and rapid (55.7±15.2 years) injection groups. The overall incidence of adverse reactions to the dye was 9.4% (47 patients) including 13.6% (34 patients) in the rapid and 5.2% (13 patients) in the slow group (P=0.001). Details related to adverse reactions are presented in Table 1. The most common adverse reactions were vomiting and nausea in the slow and rapid injection groups respectively. A lower incidence of nausea (RR=0.32; 95%CI: 0.11-0.89, P=0.02) and vomiting (RR=0.10; 95%CI: 0.02-0.45, P<0.001) was observed in the slow infusion group. There was

no significant difference between the two groups in terms of the frequency of vertigo, sweating, flushing and vasovagal reactions. No instance of moderate or severe adverse reactions was encountered in any of the study groups. None of the reactions occurred after discharge of the patient from the eye clinic.

Table 1 Incidence of adverse reactions in the rapid and slow injection groups

Adverse Reaction	Rapid injection F (P±SE)	Slow infusion F (P±SE)	*P value
Nausea	15 (6%±1.5%)	5 (2%±0.8%)	0.02
Vomiting	18 (7.2%±1.6%)	2 (0.8%±0.56%)	<0.001
Vertigo	2 (0.8%±0.5%)	3 (1.2%±0.6%)	0.653
Vasovagal reaction, sweating, flushing	0	3 (1.2%±0.6%)	0.08

F, frequency; P, probability; SE, standard error. *Chi-square test with Monte Carlo correction.

No significant difference was observed between men and women regarding the incidence of adverse reactions, however older age was associated with a decreased incidence of adverse reactions (Table 2). A lower incidence of adverse reaction was observed in the slow infusion group in both men (P=0.003) and women (P=0.056).

Table 2 Regression analysis for the role of age and sex on the rate of adverse reactions

	Odds ratio (95% confidence interval)	P value
Age	0.97 (0.95-0.99)	0.029
Sex	1.26 (0.68-2.3)	0.451

DISCUSSION

The incidence of adverse reactions in FAG varies depending on the route of administration, ranging from 1% to 2% with oral[7-9] and from 3% to 20% with intravenous routes.[2-6,10,11] In this study, the overall incidence of adverse reactions to intravenous fluorescein was 9.4%. All reactions were categorized as mild; moderate and/or severe reactions did not occur. Nausea and/or vomiting occurred in 8.2% of patients, corresponding figures range from 3% to 14% in other studies.[4,12,13] In the current study ageing was associated with a lower incidence of side effects but gender had no significant effect in this regard. We observed that the quality of FAG was comparable with slow vs rapid fluorescein injection and that slow injection had no detrimental effect on early hyperfluorescence. The maximum effect of injection appeared after 60 seconds.

Some studies have reported urticaria in 0.5% to 1.2%,[4,5] and respiratory distress in 0.02% to 0.1% of patients.[5,6,12] Such reactions can be explained by different pathophysiologic mechanisms; however they are probably of the anaphylactoid type, characterized by independent IgE mechanisms that involve direct activation of mast cells and complement together with alterations in arachidonic acid metabolism.[13,14] Skin tests with fluorescein lack predictive value because the mechanism of reaction is not IgE-mediated.[15,16] Gender has not been shown to significantly affect the occurrence of adverse reactions as has been the case in this study. Death due to FAG may occur very rarely; there are reports of one death in 200,000 patients, however direct correlation with the procedure remains controversial.[5,15-17] The incidence and severity of adverse reactions has been found to be independent of the amount and concentration of fluorescein,[5,18] furthermore warming the dye does not seem to significantly alter the incidence of nausea associated with FAG.[19]

In the present study we found a significantly lower incidence of adverse reactions following slow infusion of fluorescein in comparison with rapid injection. In contrast, Chazan[20] reported a lower incidence of adverse reactions following rapid, automated and high pressure injection of fluorescein. The reason for this discrepancy seems to be due to study methodology. In the present study, injections were performed manually over 15-20 seconds in most patients, however in the study by Chazan et al, automated injections were per-

formed faster, in just 6 seconds or more. In yet another study, no significant difference was found between slow (taking more than 6 seconds) and rapid injection of fluorescein regarding the incidence of adverse reactions.[21]

Changes in plasma calcium, complement and histamine levels have been reported after fluorescein injection.[22] Our findings may be explained by greater calcium binding with slow fluorescein infusion leading to less histamine release which is an important mediator of adverse reactions to fluorescein. Further studies are warranted to evaluate changes in serum calcium, complement and histamine levels following rapid and slow fluorescein injection.

In conclusion, slow infusion of fluorescein during fundus angiography, instead of the usual rapid injection, can be an effective way to reduce the incidence of nausea and vomiting in patients whom the first phase of angiography is of little importance in diagnosis and management.

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