Original Article

Risk factors for adverse reactions of fundus fluorescein angiography

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Background: To explore the difference between the outcomes of correlations between a series of variables and adverse reactions (ARs) to fluorescein from univariate and multivariate analysis and to evaluate the nausea effects in different age groups.

Methods: A retrospective study of patients undergoing consecutive fluorescein angiography between March 2010 and February 2012 was conducted. No patients were excluded on the ground of age, presence of atopy, allergy history, previous procedures without severe allergic ARs, asymptomatic hypertension and kidney failure with serum creatinine levels lower than 250 μmol/L or with renal dialysis.

Results: A total of 829 patients were enrolled and 22.2% of them had ARs. The majority of reactions were nausea (12.1%) which occurred less when age became old (P<0.0001). When the correlations between a series of variables and ARs were assessed separately, age (P<0.0001), prior reactions (P<0.0001) and motion sickness (P=0.0062) were highly and cardio/cerebrovascular disease (P=0.0015), diabetes (P=0.0001) and renal disease (P=0.0219) were lowly related to ARs. However, when the correlations were assessed simultaneously, only age [odd ratio (OR) 0.974; 95% confidence interval (CI), 0.962–0.986], prior reactions (OR 5.596; 95% CI, 2.083–15.029) and motion sickness (OR 4.849; 95% CI, 1.583–14.856) were statistically correlated with ARs.

Conclusions: Fluorescein angiography is a safe procedure for patients who are relatively healthy but with a history of any systemic disease. Young age, prior reactions and motion sickness which are highly related to emetic events should be considered in the evaluation of ARs to fluorescein.

Keywords: Adverse reactions (ARs); fundus fluorescein angiography (FFA); risk factors

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Introduction

Factors associated with adverse reactions (ARs) of fundus fluorescein angiography (FFA) have been investigated in previous studies. Contamination that may vary in different formulations has been found related to ARs (1-3). Patients with prior ARs are shown having an obvious higher rate of ARs (4,5). Colored races have been reported more likely to suffer from nausea and vomiting than white patients (5). Temperature of the fluorescein solution has no effect on the incidence of nausea (6).

However, quite a number of results in age, gender, concentration of fluorescein, velocity of injection, anxiety, allergic history and so on are not consistent. A report found a higher complication rate in patients 10 years younger than the average patient age while two reports discovered there is no difference in age between the patients who presented reactions and the patients who had no reaction and no difference in ARs between patients aged ≥75 years and aged <75 years (7-9). One study revealed gender

is not a risk factor for the presence of ARs but another showed male patients react adversely to fluorescein more frequently than females (9,10). No significant difference in the frequency of reactions among using 5%, 10% or 25% concentration of fluorescein was observed in several studies (11-13). Meanwhile, Yannuzzi *et al.* noted that 5% fluorescein causes nausea less frequently than does 10% fluorescein (1). Fewer reactions to fluorescein with quicker, high-pressure and automated injections compared with slower manual injections was reported by Chazan *et al.* (11). Reversely, Kwiterovich *et al.* confirmed that no statistically difference in frequency of ARs in patients with either normal or slow rate of fluorescein injection (4). Lira *et al.* displayed a higher overall rate of ARs in patients with a history of hypertension and allergy (9). Oppositely, the difference in ARs between patients with a history of hypertension or allergy and those without does not reach the level of statistical significance in the results of Musa *et al.* and Kalogeromitros *et al.* (8,14).

How to assess the effect of a variable on ARs may be the key for the discrepancies. The variables may affect each other when one is being evaluated while the others are ignored. The purpose of this retrospective study was to explore the effect of a series of variables on ARs separately and simultaneously then to find out the reasonable risk factors and try to explain the previous discrepancies. In addition, we observed the risk of emetic reactions among age subgroups.

Methods

This study reviewed all the patients who had undergone consecutive intravenous FFA from 29 March 2010 to 29 February 2012 in the Department of Ophthalmology, Guangdong General Hospital, China (when patients had multiple FFAs within the period, only the first procedure was included). Patients who reported any allergic history and presence of atopy, patients who had any prior reaction which was not a severe allergic AR and patients who complained of asymptomatic hypertension and any renal problem with serum creatinine levels lower than 250 μmol/L or with which patients had been undergoing renal dialysis were not excluded from FFA. No patient was excluded on the ground of age either.

Information in the following was obtained prior to the procedure: informed consent, age, gender, ethnic group, daily smoking habits, weekly alcohol intake, prior FFAs, medication, allergic history, past medical history and actual discomfort.

As a routine, blood pressure was measured before the procedure. Steroids or antihistamines were prescribed before FFA only when patients had a need for an ocular or systemic disease and when patients were afraid of the allergic reactions to fluorescein. The patient's eyes were dilated using 0.5% tropicamide and phenylephrine compound eye drop. Fifteen minutes after a pre-injection of 3 mL of 1‰ sodium fluorescein, 3 mL or 10 mg/kg of 20% sodium fluorescein (Guangzhou Baiyun Shan Ming Xing Pharmaceutical Co. Ltd., Guangzhou, China) was injected in each patient around eight seconds. All patients were told to inform the participating doctor and nurse if they felt unwell and the doctor also reviewed each patient to see whether they suffered any discomfort during and after the procedure. Reactions were divided into mild, moderate and severe reaction and death according to the classification suggested by Yannuzzi *et al.* (13).

Chi-square test was used to find associations between the categorical variables. $P<0.05$ was considered statistically significant. The correlations between all variables and ARs were evaluated by multivariate logistic regression analysis. Odd ratio (OR) and confidence interval (CI) were calculated.

Results

As a result, a total of 829 patients who were Asian were obtained: 459 were male with a mean age of 54.5±16.6 years and 370 were female with a mean age of 56.7±16.2 years. No statistically significant difference was found between the proportions of males and females ($P=0.1566$). Ages ranged from four to ninety.

ARs occurred in 184 patients (22.2%) and the majority of reactions were nausea (*Table 1*). Twenty-four patients had two or more reactions. There were no cases of severe ARs and death. All sensitive reactions of sneezing, sensitive cough, itching eye or throat happened in patients without the outbreak of hay fever. Eleven (52.4%) of 21 patients with prior reactions experienced similar reactions again (6 of them were emetic reactions, 2 fixed drug eruption, 2 urticaria and 1 sneezing). Seven (46.7%) of 15 patients who experienced motion sickness on the way to the clinic for the procedure experienced emetic reactions during FFA.

When the relationships between ARs and variables of age, gender, smoking, drinking, premedication of steroids or antihistamines, prior reactions, motion sickness, and a history of allergy, cardio/cerebrovascular disease, diabetes, digestive disease including liver problems, nervous disorder, renal disease, respiratory disease, malignant

Table 1 Different types of adverse reactions (n=829)

Reactions	Number (%)
Mild	
Nausea	100 (12.1)
Vomiting	24 (2.9)
Sneezing	15 (1.8)
Pruritus	11 (1.3)
Patchy skin discoloration	8 (1.0)
Sensitive cough	6 (0.7)
Dizziness	4 (0.5)
Itching throat	3 (0.4)
Itching eye	2 (0.2)
Abdominal pain	2 (0.2)
Headache	1 (0.1)
Tongue numbness	1 (0.1)
Moderate	
Skin rash	21 (2.5)
Syncope	7 (0.8)
Palpitation	5 (0.6)
Transient chest tightness	1 (0.1)
Total	211 (25.5)

tumour, mental disease and miscellanea of diseases were evaluated separately, the mean age of patients with ARs was statistically significant younger than that of those without ARs (P<0.0001), and significant higher risk of ARs were found in patients with motion sickness (P=0.0062) and a history of prior reaction (P<0.0001), interestingly, lower risk were found in patients with a history of cardio/cerebrovascular disease (P=0.0015), diabetes (P=0.0001), and renal disease (P=0.0219); however, when all these variables were evaluated simultaneously with the presence of ARs by multivariate logistic regression analysis, statistically significant correlations with ARs were only revealed in age (OR 0.974; 95% CI, 0.962–0.986), motion sickness (OR 4.849; 95% CI, 1.583–14.856) and prior reaction (OR 5.596; 95% CI, 2.083–15.029), but a history of cardio/cerebrovascular disease, diabetes and renal disease (*Table 2*).

In addition, a strong statistically significant decreasing tendency of emetic reaction along with increasing age is shown in *Table 3* (P<0.0001).

Discussion

Many factors are suggested related to ARs of FFA. For evaluating the effects of these factors, multivariate analysis

Table 2 Frequency of adverse reactions (mean age) and multivariate logistic regression analysis result (n=829)

Variables	With (%)	Without (%)	P	OR	95% Wald CI
Age	49.5±17.1	57.2±15.9	<0.0001	0.974	0.962–0.986
Gender	107/459 (23.3) (M)	77/370 (20.8) (F)	0.3891	1.074	0.720–1.600
Smoking	43/153 (28.1)	141/676 (20.9)	0.0514	1.358	0.852–2.166
Drinking	26/109 (23.9)	158/720 (21.9)	0.6549	0.970	0.573–1.645
Premedication	10/34 (29.4)	174/795 (21.9)	0.5579	0.635	0.264–1.529
Motion sickness	8/15 (53.3)	176/814 (21.6)	0.0062	4.849	1.583–14.856
Prior reaction	14/21 (66.7)	170/808 (21.0)	<0.0001	5.596	2.083–15.029
Allergy history	76/321 (23.7)	108/508 (21.3)	0.4148	0.849	0.593–1.216
Cardio/cerebrovascular disease	72/410 (17.6)	112/419 (26.7)	0.0015	1.040	0.686–1.577
Diabetes	54/344 (15.7)	130/485 (26.8)	0.0001	0.716	0.479–1.069
Digestive disease	16/59 (27.1)	168/770 (21.8)	0.3451	0.993	0.514–1.918
Nervous disorder	9/52 (17.3)	175/777 (22.5)	0.3810	1.071	0.497–2.304
Renal disease	3/40 (7.5)	181/789 (22.9)	0.0219	0.354	0.104–1.202
Respiratory disease	7/23 (30.4)	177/806 (22.0)	0.3349	1.875	0.703–5.001
Malignant tumour	6/22 (27.3)	178/807 (22.1)	0.1627	1.437	0.525–3.932
Mental disease	1/8 (12.5)	183/821 (22.3)	0.3068	0.358	0.042–3.044
Miscellanea of diseases	9/41 (22.0)	175/788 (22.2)	0.9692	0.891	0.392–2.022

M, males; F, females; OR, odd ratio; CI, confidence interval.

Table 3 Frequency of emetic reactions related to age (n=829)

Age (years)	<20	20–39	40–59	≥60	P
Number of patients	26	110	316	377	
Nausea/vomiting (%)	8 (30.8)	29 (26.4)	51 (16.1)	36 (9.5)	<0.0001
CI	13.03–48.51	18.13–34.60	12.08–20.20	6.58–12.52	

CI, confidence interval.

may be the best way to avoid influence from each other. To our knowledge, risk factors educed from a multivariate analysis has never been addressed. This study demonstrated only age, prior reactions and motion sickness but gender, premedication, smoking and drinking habits, and a history of allergy and a series of systemic diseases correlated with ARs in the multivariate logistic regression analysis. The average age of patients with ARs was significantly younger than that of those without ARs. Therefore, the proportion of young patients, patients with prior reaction and patients with motion sickness must affect the overall rate of ARs in a subgroup. That is why an obviously low frequency of ARs in patients with cardio/cerebrovascular diseases, diabetes and renal diseases did not reach the level of statistical significance in the multivariate logistic regression analysis in this study because these diseases usually happen in older people. The lower risks to FFA for these patients in the univariate analysis which had ignored the age factor obviously were false positive. Also because all of these variables are not taken into account in the previous studies, it is not surprising why the reported outcomes on single possible causative factor are widely inconsistent.

Emetic reaction which is part of vasovagal reaction is the main AR during FFA. Vasovagal susceptibility is probably present in all healthy humans but may vary in genetic basis (5). During FFA patients with prior emetic reactions have been presented more like to be nauseous and vomit in previous and our studies (4,5). Vasovagal reactions also may be precipitated by many factors such as fear, severe pain, instrumentation and dehydration. So young people who are more ready for developing dehydration and generally more scared of injection and examinations would be more likely to develop emetic reaction. In fact, the frequency of emetic reaction was observed reduced alone with increasing age in this study. Musa *et al.* also found adverse events in the group aged ≥90 are less than that in the 70- to 79-year-old group, unfortunately, they did not find a significantly difference in ARs between those aged ≥75 years and aged <75 years (8). It may be owing to a higher proportion of patients with prior reactions in the older group. Motion sickness, which is induced by nystagmus belonging to an oculo-emetic reflex, certainly would aggravate its impact on emetic episodes during FFA. However, patients only with a history of motion sickness before are not more likely to be nauseous (5). In addition, chronic consumption of exogenous toxins is suggested to increase tolerance to emetogenic stimulations (15,16). Yet, no statistical correlation between smoking or drinking and adverse events was found in our study. The rates of nausea in the groups with the habits of smoking (12.4%) and drinking (13.8%) were in fact comparable with those in the groups without the habits (12.0% and 11.8% respectively).

In clinical practice, histories of allergy and severe diseases such as myocardial infarction and malignant tumour are generally viewed as a relative contraindication for FFA. Yet, until now only the relationship between ARs and a history of allergy, ischaemic heart disease including hypertension and diabetes has been discussed. Our result identified the gap in the literature in that the relationship between ARs and a history of other diseases has not been delivered. Fluorescein is excreted mainly in the urine unchanged and partly by way of liver by conjugation with glucuronide and is not directly hepatotoxic (17). Hence, FFA is relatively safe for patients with renal and liver insufficiency when their estimated glomerular filtration rate is 45 mL/min/1.73 m^2 and greater or they have undergone renal dialysis although until now there is no satisfactory method to estimate the degree of risk associated with drug in patients with chronic liver disease (18). Our study demonstrated a history of renal or liver problem and malignant tumour did not increase adverse events. Despite the result from Lira *et al.* that patients with a history of allergy, hypertension and diabetes have a higher occurrence of ARs, but which mainly are mild type, Musa *et al.* showed ischaemic heart disease does not correlate with ARs and patients with systolic blood pressure ≥160 mmHg (1 mmHg =0.133 kPa) even have a significantly lower reaction rate than those with blood pressure <160 mmHg (8,9). Kalogeromitros *et al.* revealed atopy does not increase

the ARs risk either (14). In our study a history of cardio/cerebrovascular diseases, diabetes and allergy also was not correlated with ARs. It may be explained by the fact that blood pressure regulatory genes could be oppositely affected in vasovagal reaction and hypertension and an existing allergic condition and an atopic family history do not increase the risk of an allergic reaction to a drug (19-21). Moreover, no ST-T changes or rhythm disturbances are displayed on electrocardiograms in patients including those with diabetes, cardiac diseases and other systemic diseases during FFA (22). In addition, histories of digestive disease and mental disease suggest prone to lower threshold of emetic reaction and anxiety. However, these patients did not exhibit a higher rate of ARs in this study. It is therefore reasonable to assume that FFA is quite safe for a relatively healthy patient no matter what a past medical history and allergy history he has.

The overall rate of ARs is estimated from 0.6% to 22% (3,4,14,23,24). Most of ARs are mild. The prevalence of nausea varies widely from 0.7% to 15% (3,4,11,14,24). And the main moderate AR keeps on skin rash which occurs from 0.2% to 2.0% (3,8,9,13). Our results of 25.5%, 12.1% and 2.5% of the overall ARs, nausea and skin rash were at the high end of or beyond previous ranges. Asian ethnic group, pre-injection of 1‰ sodium fluorescein, a relatively higher size of young patients and patients with prior ARs, the physician's careful observation of any minimum clinical abnormality that is not reported by patients and the conventional review by asking patients whether they experience side effects that are not readily observable were suggested to contribute to the higher rates (5,13).

In conclusion, FFA is a relatively safe procedure. A history of allergy and severe systemic diseases which are relatively under controlled should not be viewed as a contraindication. The most common AR, emetic reaction, is correlated with age, prior reactions and motion sickness. These risk factors should be considered in future study on ARs to the dye. Multivariable analysis is also recommended to assess risk factors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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