ROLE OF FUNDUS FLUORESCIN ANGIOGRAPHY IN EVALUATION OF RETINAL DISORDERS

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ABSTRACT

BACKGROUND

Retinal disorders are the leading cause of legal blindness in the age group of 20 to 65 years. Approximately 18 million people in India have severely impaired vision due to retinal diseases. It has been nearly 40 years since the principle and technique of fluorescein angiography were first described. The procedure has now become standardized and has found a regular place in routine diagnosis of fundus disorders. This study was undertaken to assess and evaluate the role of fluorescein angiography and underline its advantages over other conventional methods of ophthalmoscopy in the evaluation of posterior segment diseases.

MATERIALS AND METHODS

A prospective study was done which included 40 patients who attended the OPD during the study period. Detailed history was taken from the patient and a thorough ocular and systemic examination was done. All patients were examined by conventional methods of ophthalmoscopy (CO) followed by a fluorescein angiography. Patients were advised necessary ocular and systemic treatment. Patient was referred to a vitreo-retinal surgeon (whenever indicated).

RESULTS

40 cases were analysed and sub-divided into 3 categories of macular disorders, retinal vascular disorders and inflammatory conditions. FA altered the diagnosis in 13.34%, 50% and 12.5% cases while categorized the lesions in 53.34%, 12.5% and 62.5% cases respectively. Incidence of side effects was 22.5% of which nausea (44.5%) and vomiting (22.25%) were the most common. Incidence of side effects was similar in all age groups, both the sexes with no gender bias and no predilection for cases with known history of drug allergy. On statistical analysis, FA proved to be a far superior diagnostic modality.

CONCLUSION

FA can help to detect cases beyond the reach of clinical ophthalmoscopy. FA is of immense value in diagnosing new vessels, planning for photocoagulation and categorization of lesions. CO has a good positive predictive value, but it has a low negative predictive value. Therefore, clinically negative cases should be advised FA. FA is a safe procedure with minor side effects. Nausea and vomiting being most common.

KEY WORDS

Retinal Diseases, Fluorescein Angiography, Altered, Categorized, Side Effects, HTN, CSR, PDR, ARMD, CSME, CRVO

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BACKGROUND

It is said that the eyes are the mirror of the soul and there is lot of truth in it. Your eyes are the doorway to your heart. They reflect your emotions and your inner being. A lot can be concluded from the expression of your eyes. Thus, it is no wonder that eyes have been the source of inspiration to poets, authors, and artists since time immemorial.

The eyes may be windows to the soul, but the retina is the brain's window to the world. When the retina is diseased, vision is seriously affected and may get entirely lost, if the problem is not addressed quickly. Fundus disorders are According to WHO, 38 million people are blind due to eye

disease. Among these 38 million blinds, majority are in 15-49 increasingly becoming a common cause of permanent and yet avoidable cause of blindness. They carry a high risk of ocular morbidity in all age groups, years and 50 or above age groups. More than 50 % of world's blind live in developing countries. One fifth of total blinds lives in India: 8.9 million. (8-9 blinds per 1000 population.) According to major population-based survey (NPCB) and one rapid assessment of avoidable blindness (RAAB) the blindness due to posterior segment disease is 4.7% - NPCB (2001-2002) and 3% - RAAB (2006-2007) in India. 3.2 million (7%) due to Age Related Macular Degeneration (ARMD) and 1.78 million (4%) due to Diabetic retinopathy have severely impaired vision. Retinal disorders are one of the major causes of blindness. Visual outcome varies from full recovery to complete blindness with physical and psychological loss and enormous economic burden on the society. Thus, diagnosis and management of fundus disorders should be given high priority.^{(1),(2)}

For over 30 years, fundus photography and fluorescein angiography have been extremely valuable for expanding our knowledge of anatomy, pathology and pathophysiology of the retina and choroid, and have aided the diagnosis, helps in identifying the cause of the pathology and monitoring of the

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treatment of retinal vascular, macular disorders and chorioretinal diseases.^{(3),(4)}

Recent technological advances in digital imaging- notably fundus camera with electronic flash and computer analysis have added a new dimension to the clinical and research applications of fluorescein angiography.^{(5),(6)}

Indications for Fluorescein Angiography^{(7),(8)}

Diagnostic:

1. To obtain detailed information about vascular flow.
2. To characterize a lesion as local or diffuse.
3. Differentiate between papilloedema and pseudopapilloedema.
4. To diagnose a choroidal pathology when other methods are inconclusive.
5. To differentiate choroidal and retinal tumours.
6. To obtain serial studies of the fundus and disc.
7. To perform genetic case studies.

Therapeutic

1. To evaluate the efficacy of treatment.
 - a. After laser photocoagulation in diabetic and hypertensive retinopathy.
 - b. After laser photocoagulation in CSR.
2. To locate and define the lesions for further treatment.
3. In treatment of tumours.
 - a. Retinal angiomas.
 - b. Retinoblastoma.
 - c. Malignant melanoma.

Normal Angiogram⁽⁹⁾

After fluorescein is injected into the antecubital vein, the time it takes to reach the eye depends upon the patient's arm-to-retina circulation time. This is typically 12 to 15 seconds. A delay in the arm-to-retina time may reflect a problem with the fluorescein dye injection or circulatory problems with the patient including heart and peripheral vascular disease.

Angiogram consists of the following overlapping phases-

- The Choroidal (Pre arterial) phase
- Arterial phase
- Arteriovenous phase
- Venous phase
- The Recirculation phase
- The Late or Elimination phase

Abnormal Fluorescein Angiographic Patterns⁽⁹⁾

- Hyperfluorescence.
- Hypofluorescence.
- Retrofluorescence.
- Fluorescein leakage.
- Fluorescein pooling.
- Fluorescein staining.
- Pseudofluorescence.
- Autofluorescence.

The study was undertaken to assess and evaluate the role of fluorescein angiography and underline its advantage over other conventional methods of ophthalmology in the evaluation of posterior segment diseases.

MATERIALS AND METHODS

The study was conducted in the outpatient Department of Ophthalmology at Tertiary hospital, Andhra Pradesh from Oct 2016 to Oct 2017. Approval for the study protocol and clearance were obtained from the ethical review committee of the institute. A total number of 100 cases were selected for the study and the patient data was categorized into age, sex, history of drug allergy and systemic illness was analysed.

Study Design

Prospective Observational Study.

Inclusion Criteria

All healthy adult patients with a fundal pathology were included in the study.

Exclusion Criteria

1. Very old patients.
2. Pregnant women.
3. Non-compliant patients who were not able to follow instructions.
4. Immunocompromised and debilitated patients.
5. Patients with known hypersensitivity to the dye.
6. Patients with renal insufficiency and cardiovascular diseases.
7. Children < 5 years of age.

A thorough and detailed history was taken of the selected patients. Complete ophthalmic and medical history was noted with special emphasis on history of drug allergy and systemic illness. Complete ocular examination including visual acuity, intra ocular pressure measurement, slit lamp biomicroscopy for both anterior and posterior segment evaluation was done.

Fluorescein Angiography

Consent Patients were explained in detail in their own vernacular language about the condition of the eye, the procedure and purpose of fluorescein angiography and possible side effects after which an informed consent was taken.

Investigations

The following investigations were performed- Complete haemogram, Urine - Albumin and sugar, FBS/RBS/PPBS (if required), and special investigations like ECG, RFT, Lipid profile Glycosylated Hb are done in relevant cases.

Procedure

Patient's pupils were dilated with a combination of 5% phenylephrine and 1% tropicamide 20-30 minutes prior to the procedure. An intravenous or intradermal test dose of the dye was given 10 minutes prior to the procedure. A 21 gauge scalp vein set was put in the antecubital vein. Patient was seated in front of the fundus camera and the 5 ml 10% Sodium fluorescein dye was injected.

It usually takes 6-8 sec for the dye to enter the retinal circulation. Pictures are taken after 5-8 sec in the young and 12 sec in the older population. Photographs were taken at 0.5 secs. intervals for the next 10-12 secs. thereafter interval extended to 2-3 sec. After this sequence the patient is asked to wait for at least 5-10 min, then late frames are taken. This

makes end of recording and the patient should be warned about the temporary discolouration of the skin and urine. The entire photographic process usually lasts for 10 to 15 minutes. Patient's pulse and general condition were monitored by the anaesthetist all throughout the procedure and any adverse reaction was noted.

After the Procedure

- Patient was made to lie down and rest for 30 minutes.
- Patient was explained about the change in colour of urine and skin.
- The findings were recorded in fundus drawings in the patient's case-sheet and analysed.

Statistical Methods

The study patients were described according to their demographic profiles such as age, gender, occupation, risk factors, prior use of drugs and clinical characteristics. The statistical procedures were performed by the statistical package namely IBM SPSS statistics-20.

RESULTS

Totally 100 cases which presented to the outpatient department with fundus pathology were evaluated both by ophthalmoscopy and FA. In this study of 100 cases, 62 patients were males and 38 cases were females. A total of 39 cases of macular diseases (39%), 42 cases of retinal vascular disorders (42%), 17 cases of inflammatory disorders (17%) and 2 cases of optic nerve drusen were analysed.

On analysis of retinal vascular disorders, there were 20 cases of diabetic retinopathy (47.61%), 9 cases of hypertensive retinopathy (21.43%), 11 cases of venous occlusive disease (26.19%) and 2 case of arterial occlusive disease (4.76%). Some cases had significant clinical features of 2 entities and were considered in both groups.

In this study, 5 cases (25%) cases were proliferative, 12 cases (60%) were non-proliferative and 3 cases (50%) were found to have maculopathy. Some cases had clinical features of more than one sub-type and were analysed in both groups.

13 cases of ARMD (33%), 13 cases of macular oedema (33%) and 13 cases of macular dystrophies (33%) were analysed. The incidence of dry ARMD was 61.54 % and wet ARMD was 38.64 %. In our study, incidence of serous oedema was 61.54 % and cystoid was 38.64 %. All the 5 cases of dystrophy were hereditary (100%).

FA confirmed the diagnosis in 15 cases (33%), altered the diagnosis in 21 cases (13.34%) and categorized the lesion in 21 cases (53.34%). FA is a superior tool in categorizing the lesions in macular disorders although diagnosis may be made ophthalmoscopically in a significant number of cases.

In the series on inflammatory diseases, 7 cases (41.18%) of retinal vasculitis, 6 cases (35.29%) of posterior uveitis and 4 cases (23.53 %) of optic nerve diseases were analysed.

FA was more accurate in categorizing the lesion in 10 cases (58.82%), altering the diagnosis in 3 cases (17.65 %) and confirming diagnosis only in 4 cases (23.53 %). FA is important for diagnosis but more specific for categorizing the lesion to start accurate treatment in inflammatory diseases.

Nausea was the most common side effect seen in 44 % of cases and vomiting was seen in 22% of cases. Incidence of grievous side effects like vasovagal reaction (11%), itching (10%) and skin eruptions (12%) was very low.

Among 100 cases, 12 cases had previous history of drug allergy, 88 cases had no history of drug allergy.

Analysis of Comparison Between Clinical Ophthalmoscopy and FA

- 32 patients were detected positive by both diagnostic modalities.
- A high percentage of cases detected positive by ophthalmoscopy are confirmed positive by FA.
- On the contrary, a high percentage of cases detected negative by ophthalmoscopy present as positive by FA indicating low negative predictive value.
- A very high percentage of cases although diagnosed positive by ophthalmoscopy are categorized into subtypes by FA.

Figure 1. CSR. (a) Clinical Appearance of CSR, (b) FA Showing Classical "Ink-Blot Appearance"

Figure 2. Cystoid Macular Oedema. (a) Clinical Appearance of CMO (b) Late Phase Showing Classical "Flower-Petal" Appearance

Figure 3. ARMD with CNVM. (a) Grey-Green Elevation Above The Fovea, (b) FA Arterial Phase Showing 'Lacy Hyperfluorescence', (c) FA Venous Phase Showing Increasing Hyperfluorescence, (d) FA Late Phase Showing Persistent Hyperfluorescence

Figure 4. PDR with CSME. a) Hard Exudates with CSME, (b) FA Showing Late Hyperfluorescence Indicative of New Vessels

Figure 5. Ischemic CRVO. a) Classical "Splashed Tomato Appearance" (b) FA Shows Extensive Hypofluorescence Indicative of Capillary Nonperfusion and Haemorrhages with Staining of Vessels

DISCUSSION

In this study, we have examined 100 patients in whom FA and clinical ophthalmoscopy was done for detection of fundal pathologies. For analysis, they have been divided into 3 sub groups – Macular disorders, retinal vascular disorders and inflammatory disorders. Purpose of the present study is to determine practical value of FA with regards to its role as a diagnostic, confirmatory and prognostic indicator of various diseases in our country.

Macular Disorders

In our study, 39% of all cases were of this sub-type, of which 33% cases presented with macular oedema (Figure 2).

CSR

Seven cases of CSR were analysed showing leakage with progressive pooling of dye in late phase i.e., "Classical smoke-stack" pattern. FA confirmed the clinical diagnosis and the patients were advised regular follow-up (Figure 1).

Nagpal et al in their study on CSR concluded that "leakage point to be occluded by photocoagulation should be decided by a preceding FA."⁽¹⁰⁾

ARMD

4 cases of clinically diagnosed ARMD on FA showed early 'lacy hyperfluorescence' with late persistent hyperfluorescence and were diagnosed as ARMD with CNVM (Figure 3). FA clearly indicated leakage, diagnosed presence of new vessels and localized the site for photocoagulation.

Chisholm IH et al in their study stated that "position and extent of subretinal neovascular membrane can be demonstrated only by FA, even a thorough clinical examination will not give enough information."⁽¹¹⁾

Macular Dystrophies

In this present study, macular dystrophies form 33% of macular disorders. All 13 cases analysed were hereditary. On FA, 6 cases showed classical "Dark choroid" appearance of Stargardt's disease. 2 cases showed "hypofluorescent spot surrounded by hyperfluorescence" typical of Adult-onset Foveal Macular Dystrophy. All these cases were diagnosed clinically as macular dystrophies, but FA categorized them into specific entities. However, its role in the diagnosis of these diseases is limited.

Verma et al in their study at RP centre, AIIMS stated "FA as the most useful and practical approach for tracing the macular lesions with FA findings conclusive in 80% of cases."⁽¹¹⁾

Retinal Vascular Disorders

In our study, incidence of retinal vascular disorders was 42%.

HTN Retinopathy

Both clinically diagnosed cases of hypertensive retinopathy were merely confirmed on FA. Two cases of BRVO was found to have signs of HTN retinopathy on FA. FA showed tortuous vessels with dilated veins and a generalized retinal and disc oedema with collaterals. In our study, no significant difference was found in documenting vessel calibre and A-V crossing changes.

However, Sharma BK et al in their study stated that "Blood flow changes, capillary bed abnormalities and abnormal formation of vessels. New vessels and microaneurysms could not be seen on direct ophthalmoscopy but hard exudates and macular star could not be visualized on FA. Haemorrhages were indicated by presence of blocked fluorescence with equal efficacy. No statistically significant difference was found with either of the methods."⁽¹²⁾

Diabetic Retinopathy

The incidence of DR was 47.61 % of all cases of retinal vascular disorders, of which 25% cases were proliferative, 60% were non-proliferative and 15% were found to have maculopathy. Of the 4 cases, diagnosed clinically as PDR, two cases showed late leakage (Figure 4). The other two cases suspected of having new vessels showed merely the presence of collaterals on FA.

Jain IS et al in their study at PGI, Chandigarh on 44 patients stated that "Major contribution of FA is to differentiate new vessels from collaterals. Presence of nonperfusion areas and broken foveal arcades are demonstrated on FA."⁽¹³⁾

4 cases diagnosed clinically as diabetic maculopathy were confirmed and categorized as diffuse. They were advised grid macular laser. Two diagnosed as mild NPDR was normal on FA. In our study, we found that FA was useful in ruling out diabetic maculopathy especially the ischaemic type with areas of non-perfusion which are not easily recognised by ophthalmoscope.

Vascular Occlusive Diseases

11 cases of venous occlusive and 2 cases of arterial occlusion were analysed in our study. 4 cases of clinically diagnosed CRVO were categorized into sub-types i.e., ischaemic (Figure

5) and non-ischæmic on FA. 6 cases of BRVO on FA showed presence of CMO, HTN retinopathy and NVE in 2 cases each.

SS Hayreh in his landmark study in 1994 concluded that "In FA, the extent of capillary non-perfusion is a reliable criterion to differentiate the two types of CRVO."⁽¹⁴⁾

Abraham C in his study stated that "FA has not only helped in documenting findings but has been a useful aid in choosing and planning patients for photocoagulation."⁽¹⁵⁾

Inflammatory Disorders

8 cases (20%) of inflammatory disorders were analysed.

Retinal Vasculitis

7 clinically diagnosed cases of retinal vasculitis were subjected to FA. 3 cases showed classical "Telangiectasia with vascular beading, dilatation and abnormal communication" indicative of Coat's disease. 4 cases showed "non-perfusion areas with late leakage i.e. NVE" indicative of Eales disease. Malik SRK et al in his study at MAMC in 1994 concluded that "various manifestations of Eales' are ideally studied by FA. FA also helps in monitoring the regression and disappearance of new vessels during treatment and follow-up."⁽¹⁶⁾

Posterior Uveitis

6 clinically diagnosed cases of posterior uveitis were subjected to FA. 3 cases showed "multifocal areas of hyperfluorescence with pooling" indicative of VKH syndrome. The other 3 cases showed "early Hypofluorescence with late staining" characteristic of serpiginous choroiditis.

Aliza Jap et al in their study at Singapore Eye Hospital stated that "Early pinpoint peripapillary hyperfluorescence on pre-treatment FA is a useful prognostic sign in VKH patients."⁽¹⁷⁾

Optic Disc Disorders

6 clinically suspected cases of papilloedema were subjected to FA. 3 cases were diagnosed as papillitis and other as AION. FA showed consistent "Delayed filling of optic disc and choroids" characteristic of AION. 2 cases of suspected papilloedema when subjected to FA showed autofluorescence in red-free light and was diagnosed as optic nerve drusens.

Mack HG et al in their study concluded that "Delayed filling of the optic disc is a consistent feature, poor or absent filling of the choroids is a characteristic feature of AION and a useful factor to differentiate between AION and NAION."⁽¹⁸⁾

Side Effects

In our study, Incidence of side effects was 22 %. Nausea was the most common side effect seen in 44 % of cases and vomiting was seen in 22% of cases. Incidence of grievous side effects like vasovagal reaction (11%), itching (10%) and skin eruptions (12%) was very low. No statistically significant difference was found in incidence of side effects among both the sexes. incidence of side effects among all age groups was low and almost similar. Patients with known drug allergy were not found to have a higher incidence of side effects.

Kwan AS et al in their study on 898 patients concluded that "FA is a relatively safe procedure and comparable to

other intravenous radiocontrast media angiography. Prophylactic treatment, fluorescein desensitization or oral FA can be considered in high risk patients."⁽¹⁹⁾

Thus, we deduce that, ophthalmoscopy has a high positive predictive value but a low negative predictive value. Hence, FA is a superior diagnostic tool and is a necessity for valuating clinically negative fundus disorders when in doubt.

CONCLUSION

1. FFA is useful for evaluation of anatomical and functional integrity of retinal microvasculature and blood retinal barrier.
2. FA clearly delineates the areas of capillary non-perfusion (CNP).
3. FA helps in detecting neovascularization (NVE, NVD) and collaterals.
4. FA helps to analyse the macular perfusion status- ischemic maculopathies.
5. FA detects area of CNVM- in ARMD as well as other conditions like myopia, angioid streak.
6. FA helps to detect underlying cause of unexplained visual loss due to fundus pathology.
7. FA confirms the diagnosis in doubtful macular and retinal vascular disorders.
8. FA reveals activity and extent of retinal inflammatory lesions.
9. FFA helps in planning laser photocoagulation.

From above Data it is certain that

1. FFA is a dynamic procedure providing wealth of information in short time.
2. FFA is a relatively safe procedure with few side effects.
3. FFA is a superior diagnostic modality especially in doubtful fundus cases.
4. FFA also improves the accuracy of diagnosis and helps in treatment planning.

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