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A COMPARATIVE EVALUATION BETWEEN FUNDUS FLUORESCEIN ANGIOGRAPHY ANDINDOCYANINE GREEN ANGIOGRAPHY IN DIAGNOSING MACULAR DISORDERS

Ophthalmology

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ABSTRACT

Background: To compare the efficacy of Fundus fluorescein angiography (FFA) with Indocyanine green angiography (ICGA) in diagnosing macular disorders and characterize choroidal abnormality observed with ICGA
Methods: A total of 100 patients of various macular disorders, of different age group were considered. All of them were subjected to Fundus Fluorescein Angiography and Indocyanine Green angiography. The observations of FFA were compared with that of ICG Angiography.
Results: Indocyanine green angiography has helped to detect the various macular lesions at the initial stage and treat them accordingly.
Conclusion: With the current available technology ICG angiography helps to detect abnormal choroidal vessels and identify various macular disorders, and treat them at an early stage.

KEYWORDS

Macular Disorders; Indocyanine green angiography; Fluorescein angiography

Introduction

A decisive step was made in 1959 when Harald Novotny and David Alvis, two medical students from Indianapolis, established the principles of fluorescein angiography (FA) of the retina with the technical development of a fundus camera and illuminant. In January 1960, they obtained the first FA of a human retina1. FFA is basically used for evaluation of macular perfusion, permiability and proliferation abnormalities of retina. Though FFA is one of the best diagnostic modality for diagnosing retinal disorders it has its own deficiencies. Choroidal phase finishes rapidly, and choroid is either obscured by retinal pigment epithelium and sometimes by serosanguinous fluid and blood, it is difficult to study choroidal circulation only with FFA. Other methods used for diagnosis of retinal diseases are indocyanine green angiography (ICGA), fundus autofluorescence (FAF), and optical coherence tomography (OCT).

Because of the limitations of fluorescein angiography (FFA) in imaging the choroidal circulation, investigators have searched for alternative dyes to improve choroidal angiography. The most promising has been indocyanine green (ICG) dye[2-4]. In 1957 ICG was used for evaluating cardiovascular circulation in valvular and septal defects. It was used later for measuring cardiac output, blood volume, and hepatic clearence. ICGA was used in Ophthalmology for the first time by Kogure and Choromokos5. Although ICG angiography (ICGA) has been performed for more than 30 years, it has not been until relatively recent, with technologic advances in high-resolution digital imaging systems or scanning laser ophthalmoscopes (SLO) together with infrared-sensitive video cameras, that the potential clinical advantages of ICG dye over sodium fluorescein were finally demonstrated.

In 1989, Destro and Puliafito demonstrated improved visualization of choroidal neovascularization (CNV) using ICGA compared with FA in selected cases[5]. They also introduced the concept of late imaging, whereby images obtained after clearing of ICG dye from the choroidal circulation show persistent hyperfluorescent pathology against a dark background.

Indocyanine green ($C_{43}H_{47}N_2O_6S_2Na$) is a water-soluble tricarbocyanine dye with a molecular weight of 775 daltons[6]. ICG's clinical utility in fundus angiography results from its spectral properties in the near-infrared range.[4-6] Compared with sodium fluorescein, whose peak absorption and emission is in the visible spectrum, ICG has a peak absorption at 805 nm and a peak emission at 835 nm. These spectral properties result in excellent penetration of the retinal pigment epithelium, macular xanthophyll, other ocular pigment, and even blood, allowing superior viewing of the choroidal vasculature. Since longer wavelengths undergo less scatter than shorter wavelengths, visualization through media opacities is improved as well. The standard technique is to inject 25mg of dye in 5ml of water slowly and begin photographs immediately. A pre injection fundus photograph rules out any pseudofluorescence or autofluorescence. The tendency of ICG to remain intravascular facilitates visualization of the choroidal vasculature.[7] ICGA is a relatively safe procedure with few reported adverse reactions e in different areas of medical practice. It should be avoided in patients with hepatic disease, since it is metabolized mainly by the biliary system.

The current study was conducted to detect the clinical manifestations of various macular lesions, their response to fluorescein angiography, and Indocyanine green angiography, and to compare the Indocyanine green angiographic findings with fluorescein angiography to set up some characteristics of Indocyanine green angiography and for better management of such cases.

Materials and Methods

For the purpose of this study, a total of 100 patients of various macular disorders, of different age group were considered. All of them were subjected to Fundus Fluorescein Angiography and Indocyanine Green angiography. The observations of FFA were compared with that of ICG Angiography.

Only selected patients who were willing for the dual angiography, made to understand the procedure, and were included in the study. Patients with history of allergy to Iodine or Fluorescein dye, hazy media and impaired liver and renal function tests, were excluded from the study.

After taking consent, all patients underwent a complete ophthalmolog ical evaluation.

This comprised of:-

Visual acuity in both eyes, unaided and aided, both for distance and near was recorded using Snellen's chart Color vision by Ishihara Anterior segment examination by slit lamp Direct and consensual papillary reactions were tested IOP was measured by Goldmann applanation tonometer Amsler Grid charting was done to evaluate the 10 degree of visual field.

Photostress testing was carried out and the recovery time noted.
Full dilation of pupil with 1% Tropicamide and 5% Phenylephrine was done.

Direct, Indirect ophthalmoscopy and Slit lamp biomicroscopy with +90 D lens were done.

Anti anaphylactic tray was kept ready for treating any emergencies.
The procedure was explained to the patients.

Colour photograph was taken for record and comparison in future. using the Fundus Camera (FF 450 plus Carl Zeiss Fundus Camera).

Red free photograph was taken.
After getting access to a good vein, 3ml of 20% sodium fluorescein dye was injected as a bolus.

Serial photographs were taken at approximately 1 second intervals, 5-25 seconds after injections. Late photographs are taken after 10 minutes and 20 minutes if leakage is seen.

2 ml of 25mg ICG dye was injected as bolus followed, by 5ml normal saline IV. Rapid serial photographs are taken initially between 2 to 30 seconds, then at about 3 minutes, 10 minutes and 30 minutes, after modifying exciter and barrier filter for ICG.

Images were displayed on a monitor and stored in a computer for recall.

The angiographic details were studied and both were compared.

All data was then collected and analyzed.

Results

A selected group of 100 patients with various macular disorders were studied. Out of the 100 cases studied 74 were males and 26 were females. Patients were divided into two groups. Group A: - Consisted of 100 patients who under went FFA .Group B :- Consisted of 100 patients who under went ICG Angiography. For the purpose of this study the lesions were grouped as follows:

Table : 1 TYPES OF MACULAR LESIONS STUDIED

Serial No	Diseases	No of cases	Percentage
1	ARMD	54	54%
2	CSR	35	35%
3	Heredomacular degeneration	3	3%
4	Macular hole	3	3%
5	IPCV	1	1%
6	CME	2	2%
7	MWEDS	2	2%
	Total	100	100%

Table 2: AGE VISE DISTRIBUTION OF DISEASES:

Age group	No of patients	Percentage
0-10	01	1%
10-20	01	1%
20-30	10	10%
30-40	28	28%
40-50	02	2%
50-60	39	39%
60-70	13	13%
70-80	06	6%
Total	**100**	**100%**

Table 3: SEX VISE DISTRIBUTION OF VARIOUS MACULAR DISORDERS

Sex	ARMD	CSR	HMD	MACULAR HOLE	IPCV	CME	MEWDS	TOTAL
Males	31	34	02	02	01	02	02	74
Females	23	01	01	01	00	00	00	26

ARMD- Age related macular degeneration
CSR- Central serous chorioretinopathy
HMD- Heredo-macular degeneration
IPCV- Idiopathic polypoidal vasculopathy
CME- Cystoid macular edema
MEWDS – multiple evanescent white dot syndrome

Table 4: CHIEF COMPLAINTS

Srl No	Disease	No of cases	Defective Vision	Scotoma	Metamorphopsia	Strain
1	ARMD	54	54	05	49	03
2	CSR	35	35	23	32	07
3	HMD	03	03	0	01	0
4	MH	03	03	0	0	0
5	IPCV	01	01	0	0	0
6	CME	02	02	0	0	01
7	MEWDS	02	02	1	0	0
	TOTAL	**100**	**100(100%)**	**29(29%)**	**82(82%)**	**11(11%)**

All cases complained of defective vision. 29 cases (29%), presented with positive scotoma, and it was more common in CSR (23/29). 82 patients had metamorphopsia, which was commonest among ARMD and CSR patients.

TABLE 5: EXAMINATION FINDINGS

Srl No	Diseases	Visual Acuity	Amsler Grid (Positive)	Colour Vision (Defective)	Photostress Test
1	ARMD	1/60- 6/12	54	44	00
2	CSR	6/12-6/60	35	17	26
3	HMD	6/24-6/60	01	01	00
4	MH	6/12-4/60	01	00	00
5	IPCV	<1/60	0	00	00
6	CME	6/60	01	00	00
7	MEWDS	6/24	00	00	00
	Total		92(92%)	62(62%)	26(26%)

TABLE :7 : Angiography findings

DISEASES	FFA FINDINGS	ICG FINDINGS
ARMD:54 Wet – 37 Dry – 17	Classic CNVM-08 Occult CNVM-29	FOCAL SPOTS-09 PLAQUES- 14 COMBINATION-03
CSR: 35	Ink Blot -27 Smoke Stack- 08 Multiple leaks-02 Bilateral -01	Hyperfluorescent spots-21 Multifocal-09 RPED- 05
IPCV: 1	No hyper/hypofluorescence	Polypoidal lesion seen
HMD: 03	Hyperfluorescence at macula	Normal
Macular hole:03	Window defect -03	Normal
CME: 02	Flower petal pattern-02	Hyperfluorescence at macula -02
MEWDS: 02	Late hyperfluorescence -2	Hypofluorescence at macula

TABLE : 8 COMPLICATIONS OF ANGIOGRAPHY:

DYE	Nausea	Urticaria	Syncope	Anaphylaxis	Death
FLUORESCEIN	13	02	01	0	0
ICG	01	00	0	0	0

Overall, Indocyanine green angiography helped to detect a well - demarcated margin of hyperfluorescence in eyes with occult neovascularization, which was not detected by fluorescein angiography in cases of ARMD. Similarly in cases of CSR, and IPCV, the lesions were better delineated and helped to subject the patients laser photocoagulation or appropriate treatment as required.

DISCUSSION :

The management of macular disorders has undergone drastic changes over the last few decades. Indocyanine green angiography has helped to detect the various macular lesions at the initial stages and treat them accordingly. In the present study, a selected group of 100 patients with various types of macular disprders were studied. A detailed ocular examination, relevant systemic examination, was carried out in all cases. The type of macular disorders included in this study as follows:-

CSR
ARMD- CNVM
IPCV

MACULAR HOLE
HEREDOMACULAR DEGENERATION
IPCV

CYSTOID MACULAR EDEMA
MULTIPLE EVANESCENT WHITE DOT SYNDROME

We have performed digital Indocyanine green angiography using Carl-Zeiss digital camera. This technique offers enhanced image resolution, direct qualitative comparison of fluorescein angiography, image archiving, and hard copy generation. This system was useful for planning pre-operative laser strategies and monitors the adequacy of laser therapy after surgery.

In this study, various types of macular lesions consisted of age –related macular degeneration 54 cases (54%), central serous retinopathy 35 cases (35%), heredomacular degeneration 3 cases(3%), macular hole 3 cases(3%), idiopathic polypoidal vasculopathy 1(1%) case, cystoid macular edema 2casess(2%), multiple evanescent white dot syndrome 2 cases(2%). Majority of the cases belonged to 50-80 years, 58cases (58%) age group, followed by 20-40 years. Males showed preponderance in various types of macular lesions, and constituted 74 cases (74%) of total cases.

AGE RELATED MACULAR DEGENERATION: In Age Related Macular Degeneration (AMD) ICGA is helpful to study the feeder vessel, study the precise nature of vascular PED[8], which is resistant to multiple anti VEGF injections, identify polypoidal CNV, document type of CNVN (occult or type 1 beneath RPE), identify and rule out any CNV beneath haemorragic detachment, diagnosis of RAP (retinal angiomatosis proliferation) or type 3 CNV in AMD[19]. ICGA is a useful adjunct to FA in assessing presence and extend of CNVM in post laser treatment.

Choroidal ischaemia play a major role in the development of ARMD. A watershed areas are present in the macular area and chronic choroidal insufficiency cause development of CNV[12,13]. ICGA along with FFA improved the understanding of the disease process in AMD. Patz and associates noticed a delayed or irregular filling in AMD patients.[14,15] They also observed tortuous and dilated choroidal vessels. Hayashi and associates confirmed the FFA appearance of classic CNVM by ICG angiography. It was Destro & Guyer who reported the use of ICGA in studying occult CNVM. Based on ICGA, Yannuzi classified occult CNV and vascularized PED into 3 groups[9,10]. The three morphological type included focal spots, plaques (well-defined or poorly defined), and combination lesions (in which both focal spots and plaques are noted). A solitary area of CNV which is well delineated and not more than one disc diameter in size was defined as “Hot Spot” or Focal lesion. Eyes with larger area of noevascualarization with variable delineation is defined as “Plaque CNV” which can be well delineated or poorly delineated. Combination lesions are those lesion in which both focal lesions are plaques are noted.Combination lesions can be subdivided into marginal spots (focal spots at the edge of plaques of neovascularization), overlying spots (hot spots overlying plaques of neovascularization), or remote spots (a focal spot remote from a plaque of neovascularization)[17,18].

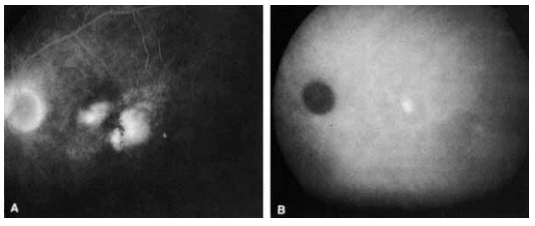

Fig. 1 **A**. Late-phase fluorescein angiogram shows ill-defined leakage in the central macular area of an eye with macular degeneration. **B.** The corresponding late-phase (23-minute) ICG angiogram reveals a discrete hyperfluorescent spot in the macula.

In the present study 54 cases of age- related macular degeneration were studied. All of them were above 50 years old. The visual acuity in these patients varied from 6/12 to 1/60. 17 patients had vision <6/60. In the present study, all 54 cases showed absent foveal reflex, 33 cases had drusens, 37 pateints showed choroidal neovacsular membrane formation.In eyes with poorly defined CNVM, digital Indocyanine green angiography provide better definition of the CNVM than parallel fluorescein angiographic studies. The potential advantage of Indocyanine green angiography over fluorescein angiography is due to the action of Indocyanine at longer wavelengths, which allows visualization through overlying blood, lipid, and pigments that may block detection of underlying choroidal pathology by fluorescein angiography. The current treatment of choroidal neovascularization is dependent on adequately visualizing the neovacsular membrane by fluorescein angiography, as the same delineates fine capillaries better than ICG Angiography. However, the importance of the later lies in the conversion of the occult to classic CNVM, so that cases of treatment are enhanced. The conversion of occult to classic CNVM in this study was 16/29 which is comparable with the pioneering study of Yannuzzi et al. However, The distribution of the different ICG types of CNVM was the same as studied by these workers. Thus the best imaging strategy to detect CNV is to perform fluorescein angiography and ICG angiography

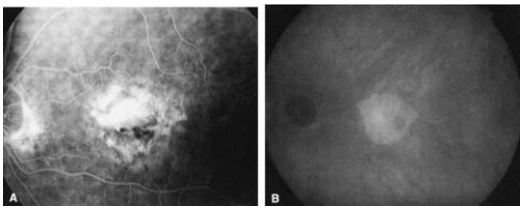

Fig. 2 **A**. Arteriovenous phase fluorescein angiogram taken from a patient with macular degeneration shows leakage in the central macula along with surrounding ill-defined, speckled hyperfluorescence. **B**. The corresponding late-phase (25-minute) ICG angiogram demonstrates a well-defined, plaque-like area of relative hyperfluores cence.

Pigment epithelial detachment (PED) in FFA show increasing hyperfluorescence. If we see signs like notches, hot spots or irregular filling, it shows neovascularization in PEDs and ICGA helped to confirm presence of new vessels.ICGA imaging can successfully guide laser photocoagulation of occult CNV and studies have proven that presence of PED is a poor prognostic factor in the treatment of AMD.

ICG also helps to identify the feeder vessel to a CNV, which can be closed with laser treatment especially when it is located inside or at the margin of a PED, though it is hard to apply vessels in PEDs.

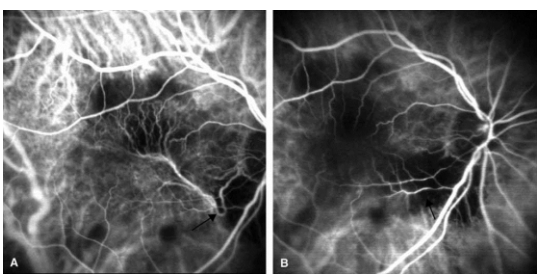

Fig2: ICG showing feeder vessel(A) which shows closure after PDT

CENTRAL SEROUS CHORIORETINOPATHY:

In 1967, Gass proposed that a choroidal exudative process is the basis of the neurosensory retinal detachment characterizing CSR. Studies on CSR have shown that it is associated with choroidal vascular abnormality. ICG may helps to diagnose cases of CSR. In chronic CSR, FFA may not be able to detect area or areas of leakage. ICG usually reveals choroidal leakage and dilated and abnormal choroidal vessels. ICG helps to diagnosis multiple areas of choroidal hyperpermeability which may not be seen in FFA. Sometimes IPCV may masquerade as chronic CSR[20,21]. It also act as a guide in PDT treatment or giving microppulse to these leaking areas.

In the present study 35 cases were studied. 33 cases were between the age group of 21-40 years. 34 cases in the present series were males, which were comparable with the similar ratio seen in the other studies. All the 35 patients complained of defective vision, visual acuity was between 6/12 -6/60. 23 had positive scotoma and 32 complained of metamorphopsia. Fluorescein angiography revealed single leak in 33 cases and multiple leaks in 2 cases and bilateral leakage in 1 case. It was observed that ICG in CSR can reach the subretinal space through the RPE defect. ICG leakage was seen corresponding with the fluorescein leakage points in 27 cases (77%). In 8 cases multiple areas of leakage was detected which could not be detected by FFA, where as

in 5 cases it was bilateral. This is consistent with the findings of Hyashi et al(80%), and Scheider et al (79%).

IDIOPATHIC POLYPOIDAL VACSULOPATHY:

IPCV is an ICG entity. PCV is characterized by reddish orange, polypoidal structure which develops because of the abnormality in the choroidal circulation and more commonly seen in blacks and Asians. ICGA shows a distinct network of vessels within the choroid, which fills before the retinal vessels at a slow rate, in the peripapillary, macular or extra macular areas. They leak slowly and become increasingly hyper fluorescent with washout or disappearance in the late phase. The late characteristic staining of occult CNV is not seen in PCV. The same was the finding in this study too and FFA cannot pickup a lesion that is beneath the haemorrhage. ICG angiography not only aided the diagnosis but helped in the treatment by laser photocoagulation (photo dynamic therapy) subsequently.

Conclusion :

We believe that ICG angiography is playing a considerable clinical role in evaluation of various macular disorders, especially AMD, CSR and IPCV. Our results support the conclusion that ICG angiography is a useful adjunctive test to compliment fluorescein angiography in diseases like occult choroidal neovacsularization. ICG should be performed when fluorescein angiography is inadequate for diagnosis, treatment or both.

In our cases though the sample size were small, ICG helped in reaching a correct diagnosis

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