Original Article

Role of Fundus Fluorescein Angiography in Preproliferative Diabetic Retinopathy

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Purpose: To identify subtle areas of ischemia and extent of capillary nonperfusion, not visible clinically and to differentiate intra-retinal microvascular abnormalities from neovascularization.

Material and Methods: Fundus fluorescein angiography of 25 patients having PPDR unilaterally or bilaterally was performed in eye department of JPMC from October 2001 to December 2002. Fundus fluorescein angiography was used as an important diagnostic tool to show exact location and extent of vascular changes of PPDR. Diabetic patients who had PPDR in one or both eye, clear media, no history of allergic reactions and normal renal profile were selected for fundus fluorescein angiography. Argon panretinal photocoagulation was planned in patients who already had complications of diabetic retinopathy in other eye and in patients who were unable to attend follow up visits, which is a major problem in our society.

Results: Out of 25 patients 9 patients (36%) showed areas of capillary dropout on angiogram, which were not visible on clinical examination. Intraretinal microvascular abnormalities were confirmed in 13 patients (52%) along with areas of capillary nonperfusion. Two patients (8%) were proved to have neovessels on angiogram. One patient (4%) showed no additional finding on angiogram but only confirmed the clinical findings.

Argon laser panretinal photocoagulation was performed on 24 eyes of 15 patients (60%). One patient (4%) had green laser photocoagulation around IRMA only. Nine patients (36%) were advised strict diabetic control and follow up visits to monitor progression of disease and need of treatment

Conclusion: Fundus fluorescein angiography was of the greatest assistance in showing the exact location of retinal vascular abnormalities and extent of capillary dropout, which were asymptomatic lesions, but a major threat to the sight of patient.

For over 30 years, fundus photography and fluorescein angiography have been extremely valuable for expanding our knowledge to visualize the chorioretinal circulation[1] and in evaluating retinal vascular disorders[2]. Maumence and MacLean[3] had used fluorescein in human fundus to help distinguish melanomas from hemangiomas during ophthalmoscopy. Fundus fluorescein angiography (FFA) is a well-established technique in ophthalmic practice. The common uses of fluorescein

angiography are in retinal and choroidal vascular diseases such as diabetic retinopathy, macular degeneration, hypertensive retinopathy and vascular occlusions. The angiogram is used to determine the extent of damage, to develop treatment plan and to monitor the results of treatment[4].

In diabetic retinopathy the angiogram is useful in identifying the extent of ischemia, the location of micro aneurysms, the presence of intraretinal microvascular abnormalities (IRMA) that can only be confirmed on angiogram; neovascularization and the extent of macular edema[5].

Fluorescein angiography is an excellent method to display the retinal capillaries in detail to show the pathologic changes because the retinal pigment epithelium provides a good background. FFA is not only useful for diagnosis but also to gauge the progression and management of diabetic retinopathy[4] (DR). FFA is a therapeutic guide to laser photocoagulation treatment for several retinal vascular diseases. Clinical investigations of DR are necessary using fundus photographs and fluorescein angiograms[6,7].

The objectives of this study were to identify subtle areas of ischemia and extent of capillary nonperfusion, which is not visible clinically and differentiate collaterals and IRMA from new vessels so that laser can be applied on required areas only.

MATERIALS AND METHODS

Fundus fluorescein angiography of 25 patients included in this study was performed in the eye department of Jinnah Postgraduate Medical Center, from October 2001 to December 2002. Patients older than 12 years of age suffering from Diabetes Mellitus with clear media, with or without visual symptoms and clinical fundal findings of cotton wool spots and venous changes and patients having marked visual loss but no significant findings clinically were included in this study.

Clinical data of each patient fulfilling inclusion criteria was recorded on prescribed proforma. Visual acuity and pinhole test of every patient were recoded using Snellen's chart for literate and E chart for illiterate patient. Near vision was recorded using N chart uniocularly and binocularly. Retinoscopy was done and best-corrected vision was noted. Anterior segment examination on slit lamp biomicroscope was done for corneal abnormalities, anterior chamber assessment, rubeosis iridis, pupillary reaction, lenticular changes (media clarity) and anterior vitreous pathology. Intra ocular pressure was recorded with Goldman applanation tonometer. Pupil dilation was done with 1 % tropicamide eye drops instilled in both eyes. In non hypertensive patients phenylephrine 10% eye drops were used for pupillary dilation and fundi were examined with direct ophthalmoscope, indirect ophthalmoscope, 90 diopter hand held non contact lens and three mirror contact lens on slit lamp biomicroscope. Random, fasting blood sugar and renal profile to assess kidney function were carried out.

Procedure and possible side effects were also explained to the patient. Kowa-RC-XV3 45084-fundus camera was used for color photographs and fluorescein angiography. Standard method of FFA was followed. A resuscitation tray was kept ready to manage any serious complications of FFA. Out of 25 patients 1 (4%) patient had dry throat and coughing and 1 (4%) patient had pain and discoloration at the site of injection due to extravasation of dye. No serious side effect of intravenous fluorescein was encountered.

In this study, panretinal photocoagulation (PRP) was done in patients who had severe subtype of preproliferative diabetic retinopathy (PPDR), proliferative diabetic retinopathy (PDR) in fellow eye, only eyed patients who have already lost sight in their fellow eyes due to complications of PDR and in patients who were unable to revisit for follow-up. This is the major problem in our part of society that leads the patients towards blindness.

RESULTS

Fundus fluorescein angiography was performed on 50 eyes of 25 patients having PPDR. Mean age of the patients was 53.2 ± 5.4 years (ranging from 43 to 61 years). There were 9 (36%) males and 16 (64%) females. Family history of diabetes was positive in 16 (64%) patients while 9 (36%) patients had no family history of diabetes. Diabetes mellitus was insulin dependent in 15 (60%) patients and non-insulin dependent in 10 (40%) patients. Associated risk factor like hypertension was present in 14 (56%) patients and 11 (44%) patients had no history of hypertension. All three stages of diabetic retinopathy were seen in the 50 eyes of 25 patients. Six (24%) patients were found to have PDR in one eye while PPDR in the other eye. Fourteen (56%) patients had PPDR in both eyes. Three (12%) patients had PPDR in one and background

diabetic retinopathy in the other eye. Two (8%) patients had PDR bilaterally.

In the eyes of 25 patients having PPDR in one or both eyes the most common angiographic finding was areas of capillary dropout seen in eyes of 9 (36%) patients (Fig. 1). IRMA and areas of capillary nonperfusion together (Fig. 2) were seen in eyes of 13 (52%) patients. Two (8%) cases were clinically diagnosed as IRMA were found to have profuse and progressive leakage (hyper-fluorescence) proving them to have PDR. Clinically 1 (4%) patient had micro-aneurysms, dot and blot hemorrhages scattered in all quadrants of fundus, multiple cotton wool spots, dilated and tortuous veins in both eyes. When FFA was done it only confirmed these clinical findings. Areas of capillary nonperfusion were only present at the sites where cotton wool spots were clinically seen. No specific angiographic findings for PPDR like IRMA or capillary dropout other than cotton wool spots seen on clinical examination were observed.

Panretinal photocoagulation (PRP) was performed in 24 eyes of 15 (60%) patients as shown in table 1. Out of these 15 patients, 8 eyes of 4 patients had bilateral PRP because on angiography 4 eyes of 2 patients were proved to have PDR in both eyes .Two patients had PDR in 1 eye, which had to be treated by PRP. Their fellow eyes had severe type of PPDR which were treated by PRP to prevent complications because they refused to come for follow up visits. Four patients were treated by PRP unilaterally because of the proliferative stage of the disease while their fellow eyes had PPDR clinically and angiographically so they were advised strict diabetic control and to keep follow up visits as they lived in the city.

On angiography, 14 eyes of 7 patients were found to have PPDR bilaterally; PRP was performed on 12 eyes of 7 patients as they belonged to remote areas. Seven patients (14 eyes) having PPDR were advised to keep follow up visits as they belonged to the city. One patient was found to have IRMA and capillary dropout in his left eye along the superonasal arcade. His right eye had background diabetic retinopathy. Green Laser around IRMA was done in his left eye while grid treatment was performed bilaterally as he had diffuse exudative diabetic maculopathy in both eyes. He was also advised follow up visits. Two patients having preproliferative in one and background diabetic retinopathy in other eye were also advised strict diabetic control and follow up visits to monitor progression of disease.

Table 1: Mode of treatment in 50 eyes of 25 patients

DISCUSSION

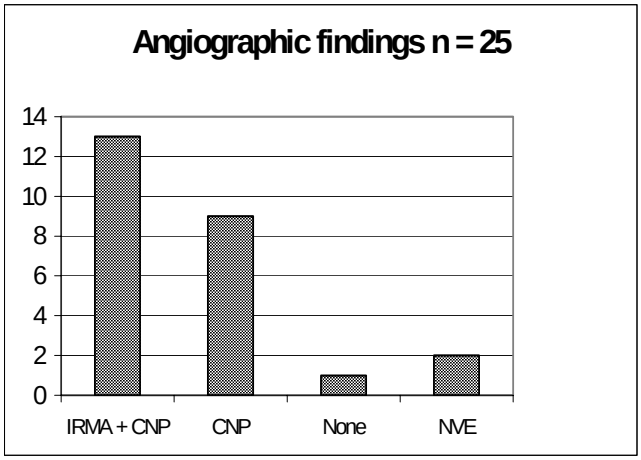
The early detection of diabetic retinopathy leads to a marked reduction of morbidity due to visual loss. Major international studies indicate that therapy is best instituted before serious complications develop. A study made by Harding et al[8] suggested that screening of diabetic retinopathy prevents blindness but because of inadequacies of current screening programs, many diabetic patients never receive treatment before developing severe visual loss. After appropriate screening, early laser photocoagulation prevents severe visual loss. Several alternative screening methods exist like direct ophthalmoscopy, various methods of fundus photography, slit lamp biomicroscopy and FFA[8]. In a study by Adhi and associates[9] diabetic retinopathy was identified in large number of patients, either focal or scatter laser photocoagulation was done after identifying leaking spots or capillary non-perfusion on fluorescein angiography.

In our study FFA had been used as an important tool to evaluate the lesions of PPDR, which were not detectable on ophthalmoscopy and slit lamp biomicroscopy, such as areas of capillary nonperfusion. IRMA were also best picked up and differentiated from neovascularisation by means of FFA.

By observing the change of fluorescence to detect and quantify areas of leakage and capillary non-perfusion. Philips and coworkers[10] believed this technique is sufficiently sensitive and robust for clinical use. FFA confirms a presumed diagnosis, determines the course of treatment and documents the finding that may change over time[11].

In 1993, Sato, Kamata, Matsui[12] classified 155 eyes (106 patients) affected by PPDR into three sub-groups on the basis of FFA. Mild type with soft exudates and without apparent non perfused areas on fluorescein angiography (39 eyes), moderate type with demonstrable non perfused areas on angiography (103 eyes) and severe type with soft exudates, venous beading and non perfused areas on angiogram (13 eyes). The courses of these three sub-groups were analyzed after one year of follow up. After one year

Treatment	Preproliferative Diabetic Retinopathy n = 37	Proliferative Diabetic Retinopathy n = 10	Back ground Diabetic Retinopathy n = 3
Follow up	22	0	3
PRP	14	10	0
Laser around IRMA	1	0	0



- IRMA = Intraretinal Microvascular Abnormalities
- CNP = Capillary Non-perfusion
- None =(NO IRMA OR CNP SEEN)
- NVE = Neovascularization elsewhere

Fig. 1: Angiographic findings in 25 patients

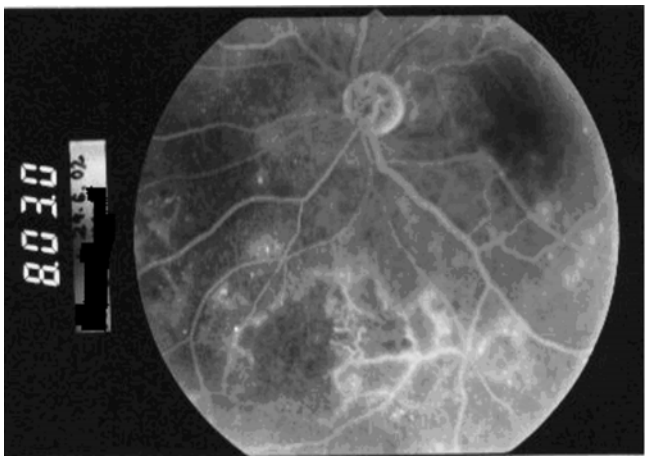


Fig. 2: Angiogram showing areas of capillary drop out and intra retinal microvascular abnormalities

the population developing PDR was 0% in mild type, 18% in moderate type and 46% in severe type.

Sato and Lee[13] conducted another study in 2002 based on their sub-classification of PPDR proposed earlier[12]. They followed up 54 patients (95 eyes) with PPDR for at least 2 years and found out that proportion developing PDR was 24% in mild type and 60% in moderate type. In mild type eyes, the rate of progression to moderate type was 56% and further progression from moderate to PDR occurred in 43%. Based on the above results they concluded that their sub-classification of PPDR on FFA could be applied to the early management of the patients with PPDR to prevent vision threatening complications.

In ETDRS[14], PPDR had 15% chances and very severe PPDR had 45% chances of developing PDR within one year. In our study FFA in eyes having PPDR evaluated areas of capillary nonperfusion in 36%, IRMA and capillary dropout in 52% of patients. All of them had scattered intraretinal hemorrhages and micro-aneurysms in all four quadrants. By comparing this study with ETDRS we found that 52% of patients had severe type of PPDR and they had 45% of chances to develop PDR within one year.

A retrospective study on reperfusion of occluded capillary bed in diabetic retinopathy done by Takahashi et al[15] reviewed 292 fluorescein angiograms of 94 eyes of 74 patients with diabetic retinopathy. Reperfusion of occluded capillary beds was observed in 65 (69%) of 94 eyes. Reperfusion was characterized by re-canalization in 22 (34%) of 65 eyes or by intraretinal revascularization in 54 (83%) of 65 eyes. In

our study intraretinal micro vascular abnormalities were observed in 52% of patients.

Several studies had been done on early laser treatment for diabetic retinopathy insisting to consider scattered PRP in severe and very severe PDR before the development of high risk SPDR[16-18]. Treatment by PRP in PPDR is indicated when patient is unable to attend follow up visits or when vision in one fellow eye has already been lost from complications of DR[5]. In our study 12 eyes of 7 patients having PPDR were treated by PRP because they refused to attend follow up visits and 2 eyes of 2 other patients having PPDR were treated by PRP as they had lost vision in their fellow eyes from complications of diabetic retinopathy.

Zhang C F[19] made a study on laser treatment for PPDR and PDR. 105 patients with preproliferative DR and PDR were treated with argon laser PRP. Among 80 patients (138 eyes) followed up for over 1 year, 50.7% had visual acuity improved by 2 lines on Snellen's chart, 39.7% had visual acuity up or down by 1 line and 10.1% had visual acuity dropped over 2 lines due to complications. Researcher had insisted on early treatment of diabetic retinopathy. In our study, 25 (50%) out of 50 eyes having pre PDR and PDR were treated by argon laser pan retinal photocoagulation to prevent vision threatening complications.

In a study by Carstocea B[20] 1050 eyes with diabetic retinopathy (70 eyes PPDR and 380 eyes PDR), were treated by argon laser photocoagulation after angiographic diagnosis. Twenty percent of treated cases had repeated photocoagulation, 70% required no repeated treatment, and 10% presented with complication of DR. Author had signified and stressed the early detection and treatment for diabetic retinopathy.

While our results are well below these studies but considering the factors of late presentation and lack of awareness of the disease in our people, these figures are fairly acceptable.

CONCLUSION

Fundus fluorescein angiograpy was of the greatest assistance in showing the exact location of retinal vascular abnormalities and extent of capillary dropout, which was asymptomatic clinically, but a major threat to the sight of patient. It picks up the asymptomatic but progressive stage of diabetic retinopathy. Severity of the disease process, which is not seen or assessed clinically, can be judged by means of FFA. Screening of diabetic population and our elderly population to detect undiagnosed diabetic retinopathy should therefore be undertaken. Laser treatment can be performed before the development of sight threatening complications of diabetic retinopathy and vision of the patients can be saved.

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