Comparison between Optical Coherence Tomography and Fundus Fluorescein Angiography in the Detection of Cystoid Macular Oedema in a Tertiary Eye Care Centre in Nagpur, Maharashtra

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ABSTRACT

BACKGROUND

Fundus fluorescin angiography (FFA) has been traditional gold standard for detection of cystoid macular oedema (CME) but nowadays optical coherence tomography (OCT) is used more often by to detect CME due to various conditions. Although FFA can assess CME qualitatively, OCT provides quantitative measurement of foveal thickness. The purpose of this study is to compare sensitivity of FFA and OCT for detection of CME and know the etiological distribution of CME and the ability of FFA and OCT in diagnosing CME in different aetiologies.

METHODS

A hospital based prospective observational diagnostic study was conducted in tertiary eye care centre in central India on 143 eyes of 103 patients. FFA and OCT findings in patients of CME diagnosed provisionally on fundus examination were studied.

RESULTS

Of total 103 patients studied, maximum patients 20 (19.42 %) were in age group of 55 - 59 years whereas minimum 6 (5.83 %) were in age group of 40 - 44 years. In 103 patients, 61 (59.22 %) were males and 42 (40.78 %) were females. Both eyes were involved in 41 (40.78 %) cases. Most common cause of CME was non-proliferative diabetic retinopathy (NPDR) 52 eyes (35.86 %), followed by branch retinal vein occlusion (BRVO) 32 eyes (22.06 %), then proliferative diabetic retinopathy (PDR) 14 eyes (9.6 %), central retinal vein occlusion (CRVO) 13 eyes (8.96 %). CME on OCT was seen in maximum of retinal vein occlusion patients - CRVO (84.61 %) and BRVO (84.37 %). Of 145 eyes, 114 (78.32 %) eyes had CME.

CONCLUSIONS

Most common cause of CME was NPDR followed by BRVO, PDR and CRVO. Sensitivity of OCT in comparison with FFA was 100 % with diagnostic accuracy of 81.38 %. Hence, one can use OCT as first modality investigation for diagnosis of CME.

KEYWORDS

Optical Coherence Tomography, Fundus Fluorescein Angiography, Cystoid Macular Oedema, NPDR

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BACKGROUND

Cystoid macular oedema represents a "final common pathway" response of retina to variety of possible insults. It has been reported with inflammatory conditions, vascular problems, inherited diseases like retinitis pigmentosa, post-operatively, tractional problems, tumours and use of medications such as epinephrine but its most common setting is following cataract surgery.[1]

CME is accumulation of fluid in the retina between outer plexiform layer and inner nuclear layer around fovea, which results in formation of cysts.[2] Clinically, CME is seen best using slit lamp and either contact lens (e.g. Goldmann lens) or a handheld non-contact lens. Fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) are much better than clinical examination to detect CME.[1]

On FFA, appearance of CME is relatively well defined as petaloid or honeycomb like pattern of hyperfluorescence as a result of dye pooling in cystoid spaces. Although FFA has been traditional gold standard for detection of CME. It is invasive, has adverse effects. OCT is imaging modality capable of providing high-resolution cross-sectional images of neurosensory retina. As OCT is non-invasive, it is quickly adapted by clinicians for assessment of patients with CME. Certain conditions may demonstrate significant intraretinal cystoid spaces on OCT without leakage on FFA. Conversely, investigators have also described cases of CME that appear only on FFA and not on OCT. The advent of high speed, spectral domain OCT (3D-OCT) has allowed more complete coverage of macular area via dense raster scanning & with higher axial resolution that provides higher sensitivity in detection of macular abnormalities.[3]

OCT findings of CME include diffuse retinal thickening with cystic areas of low reflectivity more prominently in inner nuclear and outer plexiform layers.[4-6] Although FFA can assess CME qualitatively, OCT provides quantitative measurement of foveal thickness. Therefore, pathophysiologic aspect of CME can be determined by FFA and its anatomical features such as the extent of retinal thickening and the retinal layers involved can be assessed best using OCT. Previous studies have shown that both FFA and OCT are highly sensitive in detection of CME of various aetiologies, with OCT superior to FFA according to certain parameters.[7]

Objectives

Current study was undertaken to evaluate the utility of OCT for diagnosing cystoid macular oedema, to know the etiological distribution of cystoid macular oedema and to know the ability of FFA and OCT in diagnosing CME in different aetiologies.

METHODS

The present hospital based prospective observational diagnostic study was conducted from November 2014 to October 2016 in tertiary eye care centre in central India. FFA and OCT findings were studied in total 145 eyes of 103 patients who were diagnosed to have CME on fundus examination. The study period was 2 years. Patients with relatively clear media and who were fit to undergo FFA were included in the study. Patients allergic to dye, patients having fixation difficulties, pregnant women and patients having non-leaking CME were excluded from study.

Ethical committee approval was obtained. In all patients, detailed history was followed by assessment of uncorrected and best corrected visual acuity on Snellen's chart, slit lamp examination, fundus examination with +90 D lens, indirect and direct ophthalmoscopy. All routine blood investigations viz blood sugar fasting and postprandial, haemoglobin, HbA1C, lipid profile, urine albumin, kidney function tests, blood pressure, electrocardiogram (ECG) and physician's examination was done. Written informed consent was taken. All patients underwent FFA and OCT in same visit and the results were analysed. FFA was analysed for hyperfluorescence in macular area and OCT was analysed for type of macular oedema.

Before doing FFA, fluorescein sensitivity test was done & emergency tray was kept ready. FFA was done using 3 ml of 20 % sodium fluorescein dye. Pre-injection fundus photos of both the eyes were taken and after injecting dye multiple images were taken up to late venous phase.

OCT was done using spectral domain OCT using raster scan.

FFA results were graded into petaloid/honeycomb type of fluorescence, other types including diffuse OCT results were graded into cystoid oedema, non-cystoid oedema (including diffuse retinal thickening, spongiform oedema, serous oedema) and no oedema. Petaloid fluorescence cases on FFA and cases having cystoid spaces on OCT were taken as positive for cystoid macular oedema. Results were analysed statistically.

Statistical Analysis

Statistical analysis was done by using Epi Info software version 6. Continuous variable (age) was presented as mean ± SD. Categorical variables (sex, aetiology) were expressed in actual number and percentage. Sensitivity was calculated for OCT compared to gold standard test FFA done to diagnose cystoid macular oedema. FFA and OCT were compared and kappa agreement was calculated. P value of < 0.05 was considered clinically significant.

RESULTS

Of total 103 patients studied, maximum patients 20 (19.42 %) were in age group of 55 - 59 years whereas minimum patients 6 (5.83 %) were in age group of 40 - 44 years. Age range was 30 - 78 years and mean age was 55.54 ± 10.12 years. In 103 patients, 61 (59.22 %) were males and 42 (40.78 %) were females. M : F ratio was 1.45 : 1.

Of total 145 eyes of 103 patients, right eye was involved in 37 (35.92 %) and left eye in 27 (23.30 %) and as disease was bilateral in some patients, both eyes were involved in 41 (40.78 %) cases in our study.

If both eyes had CME, then both eyes were included as in most of the cases of DR and all cases of age-related macular degeneration (ARMD). Most common cause of CME was NPDR 52 eyes (35.86 %) followed by BRVO 32 eyes (22.06 %) then PDR 14 eyes (9.6 %), CRVO 13 eyes (9.6 %). Rest of the causes include uveitis 12 eyes (8.27 %), ARMD 10 eyes (6.89 %) and other including epiretinal membrane (ERM), choroidal neovascular membrane (CNVM), post-operative cases of cataract surgery 12 eyes (8.27 %).

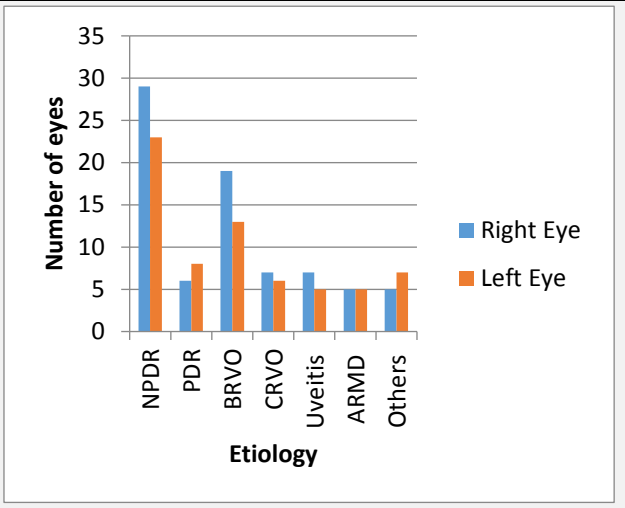

Figure 1. Eye Distribution According to Aetiology.

Amongst 145 eyes, 89 eyes were of 61 males and 56 eyes were of 42 females. In all aetiologies, males were more than females except uveitis and BRVO in which females were more.

Petaloid type of hyperfluorescence was seen in total 87 (60 %) cases of which maximum patients (75 %) belong to BRVO and minimum (50 %) belong to PDR, ARMD cases.

Sl. No.	Diagnosis	Petaloid Hyperfluorescence	Other Type of Hyperfluorescence	No Hyperfluorescence	Proportion Positive
1	NPDR	30	22	-	57.69 %
2	PDR	7	7	-	50 %
3	BRVO	24	8	-	75 %
4	CRVO	8	4	1	61.53 %
5	Uveitis	7	5	-	58.33 %
6	ARMD	5	2	3	50 %
7	Other	6	5	1	50 %
	Total	**87**	**53**	**5**	**60 %**

Table 1. FFA Pattern in Different Aetiologies (n = 145)

Cystoid oedema on OCT was seen in maximum of retinal vein occlusion patients - CRVO (84.61 %) and BRVO (84.37 %). Uveitis patients had cystoid as well as non-cystoid component of macular oedema. Of all, ARMD patients had only 60 % cases of CME. Other type of pattern on OCT was non-cystoid included diffuse, spongiform, serous. Out of 145 eyes, 114 (78.32 %) eyes had CME. Difference in aetiologies for detection of CME by OCT was not statistically significant.

In all aetiologies, OCT detected more cases than FFA. Amongst 145 eyes, cases (patients with cystoid macular oedema confirmed with FFA) missed by FFA but detected by OCT for RVO, ARMD, DR were 15.79 %, 16.67 % and 27.45 % respectively. FFA missed 30 % cases of CME due to other causes.

Sensitivity of OCT was more as compared to the gold standard test FFA in detecting cystoid macular oedema. Sensitivity of OCT was 100 % and specificity was 53.44 %.

Sl. No.	Diagnosis	Cystoid Oedema	Other Type of Oedema	No Oedema	Proportion Positive (%)
1	NPDR	41	11	-	78.84
2	PDR	10	4	-	71.42
3	BRVO	27	5	-	84.37
4	CRVO	11	2	-	84.61
5	Uveitis	10	6	-	83.33
6	ARMD	6	3	1	60
7	Other	10	2	-	83.33
	Total	**114**	**33**	**1**	**78.62**

Table 2. Pattern of Macular Oedema in Different Aetiologies on OCT (N = 145)

Single Table Analysis			
	Positive FFA	**Negative FFA**	**No. of Eyes**
Positive OCT	87	27	114
Negative OCT	0	31	31
	87	58	145

Table 3. FFA – OCT Comparison Taking FFA as Gold Standard

Sensitivity of OCT in comparison with FFA was 100 % that means all cases detected by FFA were detected by OCT with diagnostic accuracy of 81.38 %. There was a good agreement between FFA and OCT in diagnosing CME. (k = 0.5794).

Parameter	Estimate	Lower – Upper 95 % CIs
Sensitivity	100 %	(95.77, 100[1])
Specificity	53.45 %	(40.8,65.67[1])
Positive predictive value	76.32 %	(67.73, 83.18[1])
Negative predictive value	100 %	(88.97, 100[1])
Diagnostic accuracy	81.38 %	(74.26, 86.88[1])
Likelihood ratio of a positive test	2.148	(1.998- 2.31)
Likelihood ratio of a negative test	0.0	(0.0-'?')
Diagnostic odds	'undefined'	('?' – 'undefined')
Cohen's kappa (Unweighted)	0.5794	0.4318- 0.7271

Table 4. FFA – OCT Comparison Taking FFA as Gold Standard

DISCUSSION

OCT has been said to provide superior morphologic information compared with colour photography and angiography. However, in most of previous studies time – domain OCT instruments such as the stratus OCT were used. The limitations of sparse scanning density of time–domain OCT coupled with unstandardized evaluation methods may reduce power of conclusions in these previous studies and may limit their applicability in an era increasingly dominated by spectral domain OCT.[3]

The clinical assessment of macular oedema may be subjective and variable. Stereoscopic fundus examination usually only detects retinal thickening of ~100 µm. Using comparison between contact lens biomicroscopy and OCT in detection of diabetic macular oedema, Brown et al.[8] found overall agreement between results of two methods to be 69 %, which was only 23 % in cases of mild foveal thickening and 85 % when eyes with mild foveal thickening were

excluded. This suggests that contact lens biomicroscopy is relatively insensitive for detection of mild foveal thickening apparent by OCT.[5]

Another well-known diagnostic approach to detect macular oedema is FFA, which is known to be sensitive method for the qualitative assessment of fluid leakage. In comparison of two methods for detection of macular oedema in diabetic patients, Ozdek et al. found that sensitivity of OCT was higher than that of FFA, especially for cystoid pattern of macular oedema.

The present study was hospital based prospective observational comparative diagnostic study conducted in tertiary eye care centre. We studied efficacy of FFA and OCT done on same visit. Amongst 103 cases, age was ranging from 30 – 78 years and mean age was 55.54 ± 10.12 years. Maximum patients were in age group of 55 - 59 years. In a study done by Kozak et al.[7] in 2008 on 654 patients in 1272 eyes, average age of all patients was 54 ± 12.1 years. In our study males were more than females with male : female ratio 1.45 : 1. In studies done by Kozak et al.[7] and Yanling Ouyang et al.[3] females were more than males.

In our study, right eye was involved in 37 (35.92 %) and left eye in 27 (23.30 %) and as disease was bilateral in some patients, both eyes were involved in 41 (40.78 %) cases. Kozak et al. (2008)[7] studied 1272 eyes of 654 patients of macular oedema with 36 unilateral and 618 bilateral cases.

In our study, out of 145 eyes most common cause of CME was NPDR 52 eyes (35.86 %), followed by BRVO 32 eyes (22.06 %) then PDR 14 eyes (9.6 %), CRVO 13 eyes (9.6 %). Other causes included uveitis 12 (8.27 %), ARMD 10 (6.89 %) and other including ERM, CNVM, post cataract surgery 12 (8.27 %). In Kozak et al. study (2008)[5] of 1272 eyes diabetes 620 (48.7 %) was most common cause of macular oedema followed by uveitis 48 (3.8 %), vein occlusion 39 (3.1 %), pseudophakia 21 (1.6 %) and others 3 (0.2 %). In study done by Yanling et al. (2010)[3] maximum patients were of ARMD. In Garcia et al. study (2010)[9] maximum patients were of RVO 54 (63 %) in which BRVO cases were more than CRVO. In Manpreet Brar et al. (2010)[10] study who studied correlation between morphological features on spectral domain OCT and angiographic leakage patterns in macular oedema included DME 47, ERM 30, RVO 14, uveitis 12, post-surgery 4 cases. Etiological distribution in different studies is different may be because region in which these studies were conducted were different.

In our study, number of eyes affected were more in males as compared to females in all the aetiologies except uveitis and BRVO in which females were more. In case of all the aetiologies, the difference was statistically significant. ($P < 0.05$). On FFA, petaloid pattern type of hyperfluorescence was seen in total 87 (60 %) of cases; of which maximum (75 %) number of cases belonged to BRVO and minimum (50 %) belonged to PDR, ARMD cases. But difference was not statistically significant in all the aetiologies ($P > 0.05$). Cases of petaloid type of fluorescence on FFA in different aetiologies in our study was NPDR - 30 (57.69 %), PDR - 7 (50 %), BRVO - 24 (75 %), CRVO - 8 (61.53 %), uveitis - 7 (58.33 %), ARMD - 5 (50 %) and other - 6 (50 %).

Cystoid oedema on OCT was seen in maximum of retinal vein occlusion patients CRVO (84.61 %), BRVO (84.37 %) and uveitis (83.33 %) patients. Of all cases, ARMD patients had only 60 % cases of CME. Rest showed non-cystoid oedema mainly diffuse thickening. Of the 145 eyes, 114 (78.32 %) eyes had CME in our study. Difference in aetiologies for detection of CME by OCT was not statistically significant ($P > 0.05$). Cases detected by OCT were more than those detected by FFA in our study which is similar to studies done by Garcia et al.[9] Yanling et al.[3] and Mona Farag.[11]

Different studies compared FFA and OCT for detection of CME in diabetic macular oedema. Ozdek et al. studied OCT – FFA correlation in diabetic macular oedema. CME was detected with OCT in 15.4 % of eyes and 40 % of which was not detected during slit lamp biomicroscopy and 63.3 % were not detected by FFA. Great discrepancy between FFA and OCT could be because of masked cystoid staining pattern in eyes with severe focal and diffuse leakage. In our study also, 51 cases of DR with CME were detected by OCT and FFA detected 37 (72.55 %) of these cases. The cause of discrepancy may be same as that given by Ozdek et al. Low detection by FFA is because diffuse leakage in some cases may be masking petaloid fluorescence.

All post cataract surgery patients including aphakic patients who did not have other etiological factor for CME showed positive results on both FFA and OCT. But results cannot be compared since many patients of post cataract surgery had other etiological factor also. Therefore, CME in those cases is regarded as because of that particular disease than cataract surgery, as cataract surgery aggravates pre-existing CME as in case of DR and uveitis.[12-17]

In our study, cases mostly undetected by FFA include DR and other causes like ERM and CNVM. In case of ERM, leakage may be very small to demonstrate CME and many studies said ERM as cause of angiographically silent CME as Mona Farag (2014).[11] Presence of exudates or blood at macula causes difficulty in case of DR, RVO and wet ARMD. In our study cases missed by FFA for RVO, ARMD, DR are 15.79 %, 16.67 % and 27.45 % respectively. Cases missed by uveitis are 30 % and in other causes are 40 % in our study.

Sensitivity of OCT is more as compared to FFA in detecting CME cases. In our study, sensitivity of FFA was 60 % and of OCT was 78.62 %. Sensitivity of OCT in comparison with FFA was 100 % that means all the cases detected by FFA were detected by OCT with diagnostic accuracy of 81.38 %. There was a moderate agreement between FFA and OCT in diagnosing CME ($k = 0.5794$). In Kozak et al. (2008)[7] study, the sensitivity of FFA was 98.7 % and of OCT was 96.1 %. They studied all types of macular oedema that means cystoid as well as non-cystoid. Hence, the results vary from our study. Our study compares well with the studies done by Yanling et al. (2010),[3] Garcia et al. (2010)[9] and Ozdek et al. as far as comparison of sensitivity of both the investigations is considered. i.e. in all these studies OCT is more sensitive than FFA in detecting CME.

Hunter et al. (2013)[12] concluded that OCT is more sensitive for detecting the presence of diabetic macular oedema in eyes with "mild" macular oedema. Several studies

have shown that spectral domain OCT has greater sensitivity for detecting macular oedema in its early stages prior to visualization by detailed ophthalmoscopy or fluorescein angiography.

There were many studies done comparing FFA and OCT in detecting CME in various aetiologies in different regions but there was no study done in central India comparing multiple etiologies.[15,18,19] This study was our effort to find out etiological distribution and most sensitive test for detection of CME.

CONCLUSIONS

In our study, most common cause of CME was NPDR followed by BRVO, PDR, CRVO, uveitis, ARMD and other including ERM, CNVM, post-operative cataract surgery cases. Sensitivity of OCT in comparison with FFA was 100 % with diagnostic accuracy of 81.38 %. Therefore, though FFA is taken as traditional gold standard for detection of CME, as sensitivity of OCT is found to be more, one can use OCT as first modality for diagnosis of CME.

Limitations of the Study

The limitation of our study was that individual sample size for different aetiologies was less therefore the results may not be generalized. Some patients had more than one etiological factor for CME thus interpretation of results was somewhat confounded similar to study done by Yanling et al. (2010).[3]

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