Original Article

Proliferative Diabetic Retinopathy Detection: Comparison of Clinical Examination, Optomap Photographs and Fluorescein Angiography

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ABSTRACT

Introduction: This study aimed to analyse the clinical retinal examination findings and undilated Optomap ultrawide field retinal imaging for the detection of proliferative diabetic retinopathy (DR) as compared to the fluorescein angiography (FA).

Materials and methods: In this retrospective cross-sectional study, five hundred and twenty-three patients diagnosed with diabetic retinopathy on dilated retinal examination underwent fluorescein angiography and undilated Optomap imaging. Fluorescein angiography and undilated Optomap images were graded by masked graders and the diagnosis was labelled either as proliferative diabetic retinopathy or non-proliferative diabetic retinopathy. Sensitivity and specificity was calculated comparing the diagnosis obtained from the dilated retinal examination and the undilated Optomap images against the fluorescein angiography image findings.

Results: Gradable quality fluorescein angiography and undilated Optomap images with a clinical diagnosis mentioned in the medical record for that particular visit were available in 980 (right eye – 656; 67%; left eye – 324; 33%) eyes of 496 patients. There were 332 (67%) males and 164 (33%) females with a mean age of 60.3 ± 9.51 years (range: 32 – 81 years). Sensitivity of clinical examination and undilated Optomap images in accurately identifying proliferative diabetic retinopathy was 63.5% and 43.5% respectively. Specificity of clinical examination and undilated Optomap images in accurately identifying proliferative diabetic retinopathy was 88.5% and 76.2% respectively. On comparison of the undilated Optomap imaging findings against the clinical examination findings, the sensitivity and specificity were 47.7% and 75.1% respectively.

Conclusion: Both clinical fundus evaluation and undilated Optomap imaging were relatively inferior to fluorescein angiography in the detection of proliferative diabetic retinopathy, which hence remains the choice of imaging modality giving scope for wider application.

Key words: Fluorescein angiography, Optomap imaging, Proliferative diabetic retinopathy, Retinal examination.

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INTRODUCTION

The hallmark in the diagnosis of proliferative diabetic retinopathy (PDR) is the identification of new vessels either at the disc or elsewhere on clinical examination or by using different invasive or non-invasive imaging techniques (Archer, 1976; Ishibazawa et al., 2016; Vaz-Pereira et al., 2020; Wang et al., 2017). Recognition of early PDR is extremely important as appropriate, adequate and timely treatment with laser pan retinal photocoagulation and/or intravitreal anti-vascular endothelial growth factor (VEGF) agents can help in the regression of the neovascular complex and thereby prevent severe vision loss due to vitreous haemorrhage and tractional retinal detachment (Writing Committee for the Diabetic Retinopathy Clinical Research Network et al., 2015). An experienced ophthalmologist or retinal specialist can detect a neovascularization (NV) during a routine dilated retinal examination but can miss small or subtle lesions, especially when there are several associated haemorrhages or the media is not clear (Corcóstegui et al., 2017). Colour fundus photography and fluoresce in angiography (FA) have been imaging techniques that have aided in the diagnosis of PDR for the last few decades (Cole et al., 2016; "Diabetic retinopathy study. Report Number 6. Design, methods, and baseline results. Report Number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the Diabetic Retinopathy," 1981; "Grading diabetic retinopathy from stereoscopic colour fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group," 1991; Norton and Gutman, 1965; Wang et al., 2017). FA detects leakage from neovascular complexes and is thus considered the imaging technique of choice for diagnosing early PDR (Norton and Gutman, 1965; Wang et al., 2017). However, FA remains an invasive technique with occasional serious dye-related complications (Lira et al., 2007). In major clinical studies like the Protocol S reported by the DRCR.net group, FA was not taken into consideration for the diagnosis or treatment of PDR (Writing Committee for the Diabetic Retinopathy Clinical Research Network et al., 2015). Thus, the application value of FA in PDR diagnosis is fast diminishing.

In recent years, there have been significant developments in non-invasive technologies like optical coherence tomography (OCT) and OCT-angiography (OCTA) for the identification of retinal NV especially at the posterior pole and diagnosis of PDR (Cho et al., 2013; de Carlo et al., 2016; Pan et al., 2018). Proliferative changes in diabetic retinopathy have also been noted even in the retinal periphery, beyond the standard ERDRS fields (Verma et al., 2020). Thus, techniques which can simultaneously image the retinal periphery and posterior pole can efficiently detect the abnormal neovascular process of PDR. Widefield non-mydriatic or mydriatic retinal imaging offer the advantage of screening up to 200 degrees of the retina (Liu and Arevalo, 2019).

One such widefield retinal imaging device is the Optos Optomap Daytona Panoramic 200Tx (Daytona, Optos®, UK) (Aiello et al., 2019). It is a confocal laser scanning ophthalmoscope that can obtain wide-field images of the retina (200°) in a single image without the need for pharmacological mydriasis and with an acquisition time of 0.4 seconds (*Optos Daytona*, 2020). It is becoming more common in teleophthalmology settings, particularly for diabetic retinopathy screening (Silva et al., 2014, 2016a). In addition to diabetic retinopathy, Optomap has been used for baseline retinal examination in a variety of ocular pathologies such as cataract and eye trauma (Khandhadia et al., 2009; Peng et al., 2016; Silva et al., 2012). In the literature, there is very little evidence reporting its sensitivity and specificity for accurately identifying proliferative lesions in DR (Ahmed et al., 2006). In this context, we compared the detection of PDR using clinical retinal examination findings and undilated Optomap ultrawide field retinal imaging to the FA.

MATERIALS AND METHODS

This study was approved by the local Institutional Review Board of a tertiary super specialty eye hospital in South India and adhered to the principles outlined in the Helsinki Declaration. Prior to the procedures, all patients provided informed consent for imaging, including FA. The study included retrospective data from 523 diabetic patients who had undergone the same procedure for diabetic retinopathy between March 2019 and February 2020. All patients had undergone a comprehensive eye examination in a hospital setting, including a dilated fundus examination using slit lamp biomicroscopy and indirect ophthalmoscopy by experienced retinal specialists (RV, CJ, and NKY), each with 10 years' experience in retinal examination. On clinical examination, the retinal specialist diagnosed PDR or non-proliferative diabetic retinopathy (NPDR) based on the presence of NV of the disc (NVD), NV elsewhere (NVE), NV of the angles (NVA), NV of the iris (NVI), vitreous haemorrhage, fibrovascular proliferation causing tractional or combined retinal detachment. When there was a clinical suspicion of NV, these patients underwent FA to identify the type of diabetic macular edema and rule out macular ischemia. Unless the clinician suspected macular edema or macular ischemia, cases with definite PDR in both eyes were not subjected to FA.

Prior to FA, retinal images were acquired using the Optos Daytona device (Daytona, Optos®, UK), which is a scanning laser ophthalmoscope with two scanning laser wavelengths: green (532 nm) and red (635 nm). A skilled technician captured the ultra-wide field Optomap non-mydriatic images just before starting the FA in auto capture mode. Patients were instructed to look through an aperture at a green central fixation target in the primary position while seated in front of the Optos instrument. An adjustable air cushion around the aperture was in contact with the subjects' orbital rim to fine-tune subject positioning and provide stability. The machine automatically captures the image once the green fixation target becomes visible and focused. The examiner could immediately view the image. The image was captured

again and again until the desired quality was achieved. Most subjects had both eye images. For analysis, the Optomap image centred at the macula with the fewest eyelash artefacts and the largest retinal area captured was chosen in JPEG format (3470 x 1498 pixels). The Optomap images were coded for each eye (with patient details masking) and sent to another retina specialist (MBT; with > 5 years of experience as a retina specialist) for classification into PDR or NPDR based on the presence of any NV or proliferative pathology. Based on the Early Treatment Diabetic Retinopathy Study classification, cases with PDR were further divided into early and advanced PDR groups ("Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group," 1991).

Fluorescein angiography images were acquired using the Spectralis™ (Heidelberg Engineering, Heidelberg, Germany) machine. After capturing the red-free filtered fundus images, a 6-second bolus intravenous injection of 3-5 cc of 10% sodium fluorescein dye (Medi Mark agencies, Royapettah, Chennai, India) was given. A series of 55° digital photographs were taken before and after the fluorescein reached the retinal circulation using active blue excitation and yellow-green barrier filters (approximately 12 seconds after injection). For about 20 seconds, photos were taken once every second in all retinal quadrants. At 5 minutes, a delayed image was obtained. The presence of NVD or NVE indicated PDR, while the absence indicated NPDR. Intraretinal microvascular abnormalities (IRMA) were found to be hyperfluorescent lesions that did not leak on FA. The identification of IRMA was not regarded as PDR. If the diagnosis on the undilated Optomap or FA images was ambiguous, a senior retinal specialist (NKY) served as the adjudicator. The study included patients with only good quality FA and undilated Optomap images and a clinical diagnosis of diabetic retinopathy mentioned in the medical record for that specific clinical visit (Figure 1).

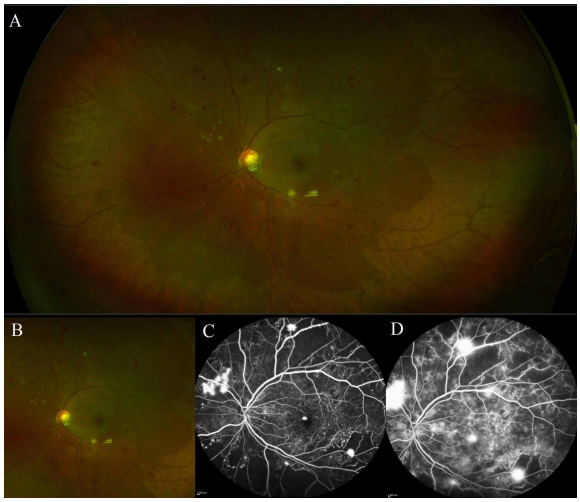

Figure 1: Optomap imaging and fluorescein angiography imaging findings in a patient with diabetic retinopathy.

Figure 1A: Optomap image (as provided to the masked grader) of the left eye in a 48-year-old male, diagnosed as severe non-proliferative diabetic retinopathy (NPDR) on dilated retinal examination by the retinal specialist. On the Optomap image, the masked grader diagnosed this eye as a case of NPDR.

Figure 1B: The cropped Optomap image of the left eye failed to identify the retinal neovascularization on the Optomap image.

Figure 1C and D: The retinal neovascularization was visible as leakage on fluorescein angiography with visible capillary non-perfusion areas.

Statistical analysis

Microsoft Excel 2016 was used for data entry and analysis. Continuous variables such as age were described using mean and standard deviation, whereas categorical variables such as gender and laterality were described using absolute values and percentages. The sensitivity, specificity, positive and negative predictive values, and accuracy of the diagnosis obtained from the dilated retinal examination and the undilated Optomap images were calculated in this study and compared to the FA image findings. The ability of a test (dilated retinal examination or undilated Optomap images) to correctly identify true-positives is referred to as test sensitivity (against the standard FA images). The ability of a test (dilated retinal examination or undilated Optomap images) to correctly identify true-negatives is referred to as test specificity (against the standard FA images). These values were used to calculate positive and negative predictive values as well as test accuracy.

RESULTS

Patient characteristics: Gradable quality FA and undilated Optomap images with a clinical diagnosis mentioned in the medical record for that particular visit were available in 980 (right eye – 656; 67%; left eye – 324; 33%) eyes of 496 patients. The study included 332 (67%) males and 164 (33%) females. The patients' average age was 60.3 ± 9.51 years (range: 32 – 81 years).

Severity of diabetic retinopathy: Eyes were classified into PDR and NPDR based on the dilated retinal examination findings, undilated Optomap imaging features and FA findings **(Table 1)**. 352 (36%) eyes were diagnosed as PDR on dilated retinal examination as against 324 (33%) eyes and 460 (47%) eyes on Optomap images and fluorescein angiography images respectively. Early PDR on dilated retinal examination was noted in 272 (78%) eyes while advanced PDR on dilated retinal examination was noted in 80 (22%) eyes. On the undilated Optomap images, early PDR was diagnosed in 230 (71%) eyes and advanced PDR in 94 (29%) eyes. Comparative analyses between clinical diagnosis, Optomap image diagnosis and FA diagnosis are described in **Table 2**. Higher number of true-positive cases of PDR were diagnosed on dilated retinal examination as

Table 1: Diagnosis of non-proliferative and proliferative diabetic retinopathy on clinical examination and different imaging modalities.

	Retinal examination	Optomap images	Fluorescein angiography images
NPDR [N (%)]	628 (64)	656 (67)	520 (53)
PDR [N (%)]	352 (36)	324 (33)	460 (47)

Abbreviations: PDR – proliferative diabetic retinopathy; NPDR - non-proliferative diabetic retinopathy

Table 2: Sensitivity analyses of clinical retinal examination and Optomap images as compared to the fluorescein angiography images.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Diagnosis of PDR between retinal examination and fluorescein angiography images	63.5	88.5	83	73.2	76.7
Diagnosis of PDR between undilated Optomap images and fluorescein angiography images	43.5	76.2	61.7	60.4	60.8

Abbreviations: PDR – proliferative diabetic retinopathy; PPV – positive predictive value; NPV – negative predictive value.

against the diagnosis on the undilated Optomap images. Comparative analysis between dilated retinal examination diagnosis and undilated Optomap image diagnosis showed relative lower sensitivity (48%) of the undilated Optomap images as compared to dilated retinal examination in the diagnosis of PDR.

DISCUSSION

The current study suggests that dilated retinal examination and undilated Optomap images are inferior to FA in detecting proliferative diabetic eye disease. FA still remains the gold standard imaging technique for diagnosing PDR.

Diabetic retinopathy screening aims at identifying patients who require a close follow up or treatment to reduce retinopathy induced severe vision loss and referral for better systemic management. Detection of early cases of PDR is essential so that timely and adequate treatment can prevent further progression of the disease and permanent blindness. Dilated retinal examination by indirect ophthalmoscopy is a simple conventional method for screening diabetic retinopathy; however, detecting subtle changes and estimating the severity of lesions can be erroneous (Wang et al., 2017). This is especially true when the specialist is not

proficient in ophthalmoscopy, when there is media haze, in patients with asteroid hyalosis and poorly dilating pupils. Our findings suggest that standard ophthalmoscopic dilated retinal examination and undilated Optomap images have a higher rate of missing NV that is essential for the diagnosis of PDR in comparison with the gold standard FA. The role of FA in diabetic retinopathy was first described by Norton and Gutman in 1965 (Norton and Gutman, 1965), and it helps to study and understand the retinal vasculature (Moise et al., 2013). It aids in the diagnosis of early NPDR and PDR, both of which can be potentially missed on clinical examination (Xie et al., 2008). Hyperfluorescent dots suggestive of microangiopathy, capillary non-perfusion areas, IRMA and fluorescein leakage either from the microaneurysms or NV are common features on FA (Wang et al., 2017). In severe diseases, it is useful to study progression and reclassify the stage of the disease (Varma et al., 2014). Therefore, FA has an added advantage in high grades of diabetic retinopathy or in whom there is a suspicion of proliferative disease. In this study, we found dilated retinal examination to be moderately sensitive and highly specific in detecting proliferative disease as against the gold standard FA. In about 37% of cases, the diagnosis of PDR would have been missed had an FA not been done. Possible reasons confounding intraretinal haemorrhage or small, subtle, flat, or anterior neovascular complexes. Another advantage of an FA is that it helps in the management plan of PDR based on the location of NV and extent of capillary non-perfusion. Eyes with posteriorly located NV can be amenable to intravitreal anti-VEGF injections alone or combination with pan retinal photocoagulation. An important consideration of FA is that it is an invasive technique and has dye related complications ranging from mild allergic reactions to very rarely death, due to anaphylaxis (Lira et al., 2007).

The Optos Optomap Daytona Panoramic 200Tx (Daytona, Optos®, UK) is gaining popularity for diabetic retinopathy screening as it provides a wide-field single capture image of the retina without pupillary dilatation. A study by Silva et al concluded that the number of ungradable eyes reduced by 81%, a two-fold increase in identification of diabetic retinopathy and a greater number of peripheral lesions identified on ultra-wide field undilated Optomap imaging compared to non-mydriatic fundus photography (Silva et al., 2016b). A study by Manjunath et al showed the sensitivity and specificity of Optomap ultra-wide-field imaging in detecting proliferative lesions to be 73% and 96% respectively in comparison to dilated clinical evaluation (Manjunath et al., 2015). On the contrary, our study showed poor sensitivity (47.7%) and specificity (75.1%) in identifying proliferative lesions on undilated Optomap images. The methodology used in the study by Manjunath et al was different compared to our study. While we provided the grader with a single exported Optomap image for grading, in the study by Manjunath et al, three steering images were obtained and viewed with the proprietary software of the

Optos machine using all the available filters and adjustments. The red and green filters allow better delineation of pathology on the pseudo colour Optomap images. Also, in the study by Manjunath et al, retinal examination was done by clinicians having different grades of clinical experience while in our study, all clinicians were fellowship trained and had a minimum of 5 years of experience. In both studies, the image was graded by an independent masked observer having sufficient experience in diabetic retinopathy grading. This discrepancy between the findings on dilated retinal examination and undilated Optomap images could also be accounted for by higher numbers of early PDR cases in the current study. Another possible reason is that dilated retinal examination is a 3-dimensional dynamic evaluation compared to an image, which therefore allows the elevated proliferations to be visible even in the presence of a hazy media. The undilated Optomap images showed poor sensitivity (43.5%) and moderate specificity (76.2%) in comparison to the gold standard FA images in detecting PDR. Thus, we found that the Optomap images were inferior to dilated retinal examination and FA in detecting proliferative DR lesions.

Our study's strength lies in the large number of eyes in whom clinical examination, FA and widefield imaging was done for the assessment of PDR in a hospital-based setting, to allow better comparison. All retinal examinations and image grading were done by clinicians with a good level of expertise in diabetic retinopathy diagnosis and grading. This study had several limitations. To begin with, the results of this study cannot be carried forward if the same methodology for PDR evaluation was used in a community-based setting. Second, we did not examine the agreement between the three examination techniques for the various degrees of DR severity. Third, we did not examine the inter-observer agreement between retinal specialists for the clinical diagnosis of PDR. In addition, we did not include cases with definite PDR on clinical examination in this study. Because the goal of the study was to look for the 'miss rate' in the detection of PDR by dilated retinal examination and undilated Optomap imaging techniques, we grouped the findings broadly into PDR and NPDR for ease of comparison. Fourth, mydriatic Optomap images may have improved image quality, particularly in the retinal periphery, resulting in a higher rate of detection of proliferative lesions.

CONCLUSION

Both clinical fundus evaluation and undilated Optomap imaging were relatively inferior to FA in the detection of PDR, which hence remains the gold standard giving scope for wider application.

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