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Original Research Article

Evaluation of the role of fundus fluorescein angiography and spectral domain-optical coherence tomography in choroidal neo-vascularization: a hospital-based study

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ABSTRACT

Background: The study was conducted to evaluate the role of fundus fluorescein angiography (FFA) and spectral domain-optical coherence tomography (SD-OCT) in choroidal neo-vascularisation (CNV).
Methods: This was a hospital based prospective study carried out in the post-graduate department of ophthalmology, SKIMS medical college, Bemina, Srinagar, Jammu and Kashmir. All patients diagnosed with CNV fulfilling the criteria during the study period w.e.f. October 2018 to March 2020 were enrolled. Visual acuity and pinhole test using Snellen's chart for literate and E chart for illiterate patient, slit lamp biomicroscope for anterior segment examination, ophthalmoscopy, including stereoscopic examination of the posterior pole, 90D examination of the fundus, Intra-ocular pressure measurement, FFA and SD-OCT was done in these patients.
Results: Diagnostic accuracy of OCT was observed with a sensitivity 79.1% (95% confidence interval (CI): 67.3-90.7), specificity 84.3% (95% CI: 74.5-92.9), positive and negative predictive values 78.7% and 85.4%, respectively, (95% CI: 65.5-95.6) and (74.8-93.4) and diagnostic accuracy of FFA was observed with a sensitivity 81.4% (95% confidence interval (CI): 70.6-93.5), specificity 82.31% (95% CI: 71.9-89.3), positive and negative predictive values 79.9% and 83.7%, respectively, (95% CI: 68.8-92.9) and (70.3-91.2).
Conclusions: FFA is the gold standard procedure for screening ARMD and detection of dry ARMD, but OCT is more specific diagnostic tool in detecting early subretinal neovascular membrane and also to assess the extent, location and activity of the neovascular membranes. This study concludes that SDOCT is highly sensitive for identifying AMD, CNV, and CNV activity and due to its non-invasive nature with no adverse effects and less time consuming can be used as 1st line of diagnostic modality and FFA be reserved for cases where SD-OCT is not helpful.

Keywords: FFA, SD-OCT, CNV

INTRODUCTION

Choroidal neovascularization (CNV) is the development of new, damaging blood vessels that grow beneath the retina in choroid and break through the barrier between the choroid and retina. When they leak in the retina, they cause vision loss. The choroidal neovascularisation is a manifestation of the diseases affecting choroid, Bruch's membrane and retinal pigment epithelium (RPE). CNV originates from the choroid and is located initially within the layers of Bruch's membrane; subsequently it may penetrate the RPE and grow under neurosensory retina. CNV may occur as an idiopathic entity or in association with number of pathological conditions like age-related macular degeneration (AMD), ocular histoplasmosis, pathologic myopia, angiod streaks, choroidal tears and in certain tumours and inflammatory diseases of choroid and retina. It can cause severe visual loss due to leakage,

haemorrhage and scar tissue formation damaging the photoreceptors and the RPE.

Risk factors

Age 50 and older, risk grows with age. This is because wet AMD accounts for most patients with CNV. People with risk factors for different eye diseases or who have an eye injury may develop CNV at a younger age. AMD is a multi-factorial syndrome with different causative factors damaging the macula and results in a common manifestation that we recognize clinically as AMD. Risk factors implicated in clinical and laboratory studies include drusen, photic injury, antioxidant and vitamin/mineral deficiency.[1-4] Neovascular type of AMD characterized by CNV occurs in older patients who are more likely to show evidence of non-specific cardiovascular problems.[5-7] Hypertension and smoking are associated with development of neovascular AMD as well as with recurrence of CNV following laser photocoagulation.[8]

The frequency of developing neovascular maculopathy in the second eye ranges between 12% and 34%.[6,7] Using Kaplan-Meir life table analysis, Strahlman et al have calculated a cumulative risk of 4%, 10% and 17% at 12, 24 and 36 months, respectively.[8] In the macular photocoagulation study (MPS) 128 fellow eyes developed CNV with a 5-year cumulative incidence rate of 28% and an estimated average annual incidence rate of 6% per year.[9]

If untreated, these neovascular processes may evolve into a hypertrophic, fibrotic, disciform scar. Retina overlying the scar loses its normal outer retinal architecture, which can lead to severe, permanent central vision loss. So, the early diagnosis and treatment is a key tool for saving patient's vision. Various methods for diagnosing CNV are fluorescein angiography, where CNV may be described as classic or occult. Two other tests that help identify the condition include indocyanine green angiography and OCT.[10]

To diagnose CNV special imaging of eye are taken. These images are taken using fluorescein angiography (FA) and OCT.

During FA, a fluorescein dye is injected into a vein in the arm. The dye travels throughout the body, including eyes. FA captures images of retinal blood vessels as the dye passes through them. The dye highlights abnormal areas, showing ophthalmologist whether there is CNV. Optic coherence tomography (OCT) scanning creates a cross section imagine of retina. This image helps ophthalmologist detect abnormal blood vessels.

The FFA images are classified into the following groups:[11-15] 1. Classic CNV, subdivided into 100% classic, classic without occult, predominantly classic with occult, or minimally classic with occult, 2. Occult CNV, subdivided as late leak of undetermined origin or vascularised PED. Retinal angiomatous proliferation (RAP) was also included, 3. Serous PED-early area definition with increasing hyper-fluorescence and 4. Non-CNV-which could be defined as: a. Dry AMD, drusen/atrophy and b. Other diagnosis-for example, retinal vein occlusion (RVO), macular hole, etc.

The OCTs were classified as to whether there was an AMD lesion (defined by (1), (2), or (3) below), and further, to try to define the type of lesion with the aid of the following features:[16-19] 1. Classic CNV-a subretinal band corresponding to the retinal pigment epithelium (RPE) and choriocapillaris which is thickened and disrupted, typically a fusiform or "cigar" shape with/without intraretinal / subretinal fluid (SRF), 2. Occult CNV-a less well defined band than classic CNV but appears to be more sub-RPE with more disorganisation of the retina and subretinal and/or intraretinal fluid (cystoid), 3. Serous PED-dome-shaped elevation of the reflective band corresponding to the RPE with an area of low reflectivity underneath, 4. Non-CNV: a. Dry AMD, drusen/atrophy-thinning of the retinal layer with reduced reflectivity of the RPE but increased reflectivity of the choroidal layer and b. Other diagnosis-for example, epiretinal membrane (ERM), macular hole.

Treatment of CNV may vary depending on the underlying disease. Treatment includes anti-VEGF drugs, thermal laser treatment or photodynamic therapy (PDT). Depending on the progress of disease, patient may receive one or more of these treatments. Another recent and most accepted modality of treatment is intra-vitreal anti-VEGFs, these target vascular endothelial growth factor or VEGF, that causes growth of abnormal blood vessels. Blocking VEGF reduces the growth of CNV, slows their leakage, helps to slow vision loss and in some cases improves vision.

Aim of the study

This study was done to evaluate the role of FFA and SD-OCT in CNV.

METHODS

This was a hospital based prospective study carried out in the post-graduate department of ophthalmology, SKIMS medical college Bemina, Srinagar, Jammu and Kashmir.

All patients diagnosed with CNV fulfilling the inclusion and exclusion criteria during the study period w.e.f. October 2018 to March 2020 were enrolled.

Inclusion criteria

All patients attending the ophthalmology OPD or admitted in the ophthalmology ward clinically diagnosed with CNV were included in the study.

Exclusion criteria

Patients with history of any retinal surgeries, laser treatment or photocoagulation therapy, retinal/choroidal detachment or manifestations of retinal trauma, intra-vitreal pharmacological intervention such as intra-vitreal anti-VEGF. Patients with hypersensitivity to fluorescein dye, renal insufficiency, pregnant women, immunocompromised status patients and patients with other vascular disorders of retina including retinopathy of prematurity were excluded from the study.

All the patients went through a standard examination protocol including: 1. Detailed history, 2. Systemic examination, 3. Visual acuity and pinhole test using Snellen's chart for literate and E chart for illiterate patient, 4. Slit lamp biomicroscope for anterior segment examination, 5. Ophthalmoscopy, including stereoscopic examination of the posterior pole, 6. 90D examination of the fundus, 7. Intra-ocular pressure measurement, 8. FFA using Carl Zeiss Meditec AG retinophotograph and 9. SD-OCT using Zeiss Cirrus HD-OCT.

The recorded data was compiled and entered in a spreadsheet (Microsoft excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages.

RESULTS

The 114 eyes of 62 patients were included in the study.

Age distribution

Out of 62 patients, 28 (45.2%) belonged to age group of 71-80 years followed by 26 (41.9%) patients who were aged 61-70 years. There were only 8 (12.9%) patients <60 years of age. The mean age the study patient was 67.8+8.91 years with the youngest one being 53 years and the eldest one 78 years of age (Figure 1).

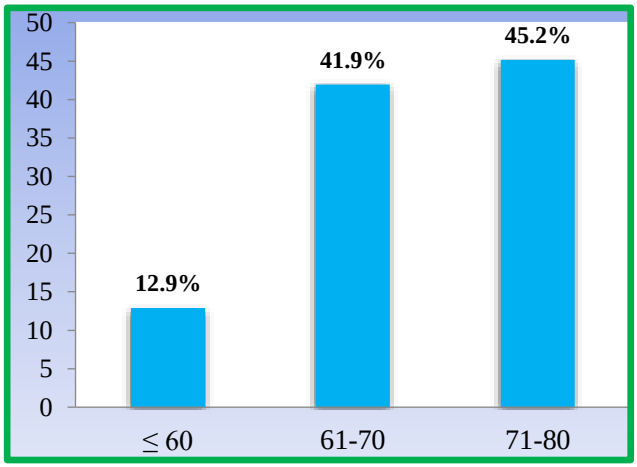

Figure 1: Age distribution of study patients.

Gender distribution

Males outnumbered females viz. 37 (59.7%) versus 25 (40.3%) (Figure 2).

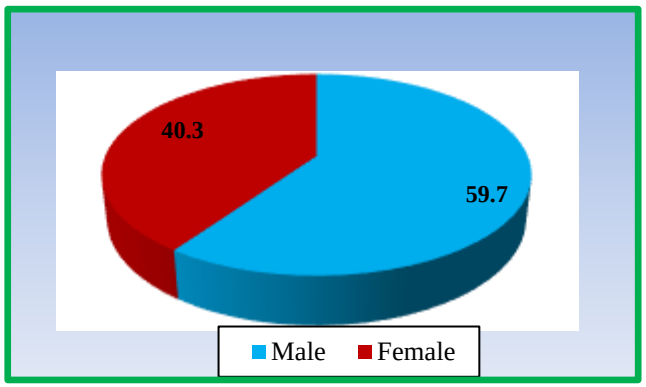

Figure 2: Gender distribution of study patients.

Presenting complaints of study patients

The 58 (93.5%) patients presented with defective vision, followed by defective vision + metamorphopsia in 3 (4.8%) and defective vision + micropsia in 1 (1.6%) patient (Table 1).

Table 1: Presenting complaints of study patients.

Complaints	No. of patients	Percentage (%)
Defective vision	58	93.5
Defective vision + metamorphosia	3	4.8
Defective vision + micropsia	1	1.6
Total	62	100

Laterality of disease in study patients

Out of 62 patients, 52 (83.9%) had bilateral eye involvement while as only 10 (16.1%) patients had unilateral eye involvement (Figure 3).

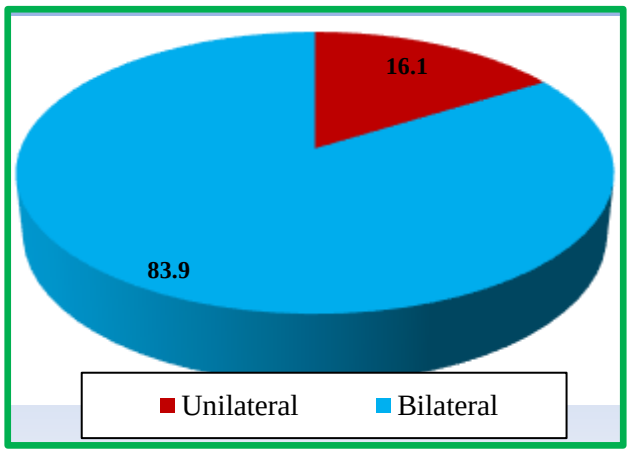

Figure 3: Laterality of disease in study patients.

Visual acuity

On Snellen chart, 12 (10.5%) patients had BCVA of 6/12-6/24 followed by 6/24-6/36 in 32 (28.1%), 6/60-1/60 in 40 (35.1%), CF 1-6 m in 20 (17.5%) and 10 (8.8%) had HM, PL, PR (Table 2).

Table 2: Best corrected visual acuity in study eyes.

Visual acuity	No. of patients	Percentage (%)
6/12-6/24	12	10.5
6/24-6/36	32	28.1
6/60-1/60	40	35.1
CF 1-6 m	20	17.5
HM, PL, PR	10	8.8
Total	114	100

Findings on ophthalmoscopy, slit lamp/90D examination and fundus photography in study eyes

Out of total 114 eyes studied, hyperpigmentation in macular area was found in all eyes followed by drusen's in 91 (79.8%), haemorrhage in 13 (11.4%), macular oedema in 9 (7.9%), geographic atrophy in 7 (6.1%) patients and cataract in 3 (2.6%) patients (Table 3).

Table 3: Findings on ophthalmoscopy, slit lamp/90D examination and fundus photography in study eyes.

Findings	No. of eyes	Percentage (%)
Hyperpigmentation in macular area	114	100
Drusens	91	79.8
Hemorrhage	13	11.4
Macular oedema	9	7.9
Geographic atrophy	7	6.1
Cataract	3	2.6

FFA findings of study eyes

Out of classic CNVM, 29 (25.4%) in were pure classic, 23 (20.2%) had predominant CNVM and 11 (9.6%) minimal CNVM. Late leak occult CNVM was observed in 17 (14.9%), RAP in 1 (0.9%), serous PED in 2 (1.8%). Drusen in patients with no CNVM in 13 (11.4%) and atrophy in 4 (3.5%) eyes (Figure 4).

OCT findings of study eyes

Classic CNVM was seen in 65 (57%) eyes, occult CNVM in 19 (16.7%) eyes, serous PED in 21 (18.4%) eyes, no CNVM (drusen/atrophy/cataract) in 9 (7.9%) eyes. There was no view on OCT 3 patients with cataract (Figure 5).

Diagnostic accuracy of OCT and FFA in diagnosis of CNVM

Diagnostic accuracy of OCT was observed with a sensitivity 79.1% (95% confidence interval (CI): 67.3-90.7), specificity 84.3% (95% CI: 74.5-92.9), positive and negative predictive values 78.7% and 85.4%, respectively, (95% CI: 65.5-95.6) and (74.8-93.4) and that of FFA was observed with a sensitivity 81.4% (95% confidence interval (CI): 70.6-93.5), specificity 82.31% (95% CI: 71.9-89.3), positive and negative predictive values 79.9% and 83.7%, respectively, (95% CI: 68.8-92.9) and (70.3-91.2) (Table 4 and 5).

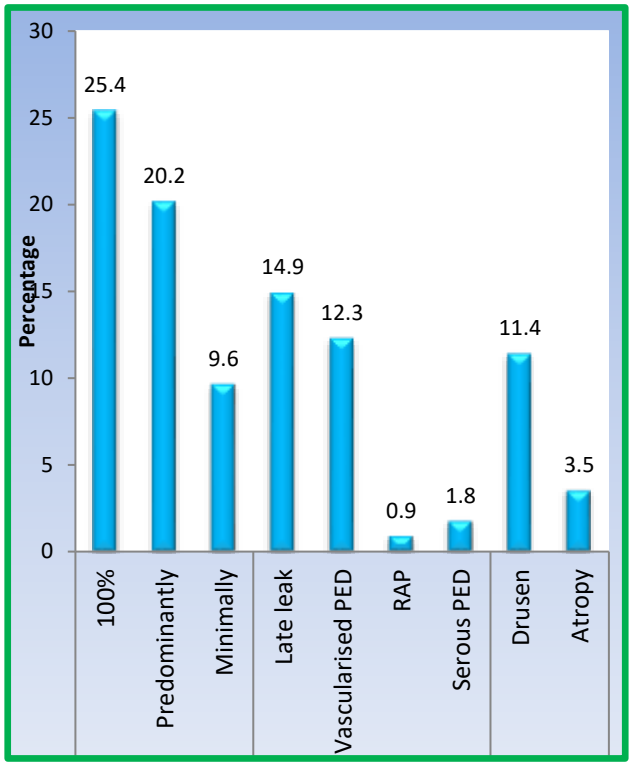

Figure 4: FFA findings of study eyes.

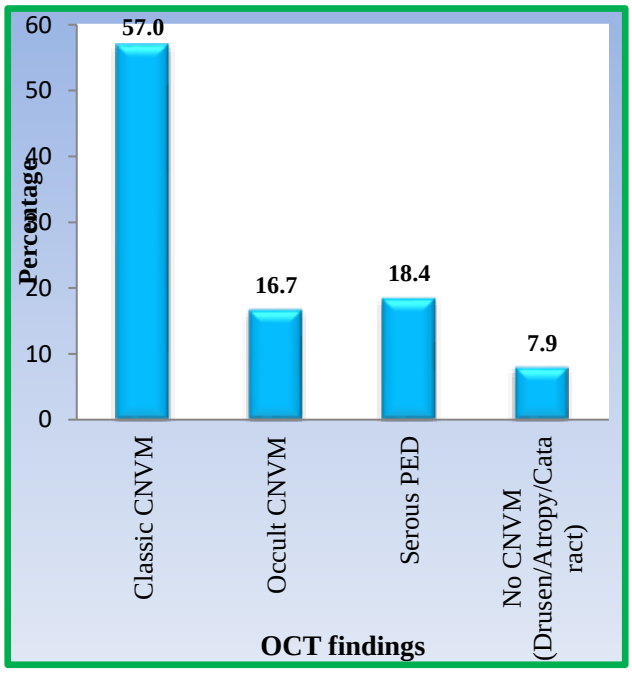

Figure 5: OCT findings of study eyes.

Table 4: Diagnostic accuracy of OCT in diagnosis of CNVM.

Parameters	Value	95% confidence interval
Sensitivity	79.1	67.3-90.7
Specificity	84.3	74.5-92.8
Positive predicted value	78.7	65.9-90.6
Negative predicted value	85.4	74.8-93.4

Table 5: Diagnostic accuracy of FFA in diagnosis of CNVM.

Parameters	Value	95% confidence interval
Sensitivity	81.4	70.6-93.5
Specificity	82.1	71.9-89.3
PPV	79.9	68.8-92.9
NPV	83.7	70.3-91.2

DISCUSSION

Conventional FFA is widely used to study retinal and choroidal vasculopathies but has limitations due to invasiveness and dye-related side effects notably nausea, vomiting and allergic reactions. OCT, on the other hand, is fast and non-invasive, and has emerged as an alternative to FFA to detect and monitor CNV. However, OCT cannot replace traditional angiography as hyperreflectivity of RPE, hemorrhage and drusens have similar signals on OCT and FFA distinguishes between these lesions reasonably well.[20]

In our study, out of 62 patients, 87% were in their 5th to 7th decade of life with a mean age of 67.8±8.91 years. Males outnumbered females viz. 37 (59.7%) versus 25 (4.3%). There were 62.9% smokers in our study. Chhablani et al conducted a study on a total 80 eyes of 57 subjects in which 32 were males and 25 females with a median age of 50 years ranging from 16-85 years.[21] The youngest and the oldest patient in our study were 55 and 90 years old respectively (mean=72.6±8.2 years). The highest number of patients were seen in the age group of 71-80 years (41.54%) followed by 61-70 years (35.38%), clearly in accordance with the establishment of the disease being a predicament of the elderly.[22,23]

In our study, 58 (93.5%) patients presenting with defective vision, followed by defective vision and metamorphopsia in 3 (4.8%) and defective vision and micropsia in 1 (1.6%) patient. In a study done by Balasubramaniam et al the most common symptom was defective vision accounting for 92%.[24] The 4% of the individuals with disciform scar had scotoma and 12% of the patients with CNVM had metamorphopsia by Amsler's grid evaluation Ryan et al.[25] Symptoms of our study are also compared with the study done by Querishi et al where the common symptom was defective vision followed by metamorphopsia and scotoma.[26]

Out of 62 patients, 52 (83.9%) had bilateral eye involvement while as only 10 (16.1%) patients had unilateral eye involvement. These results are consistent with the study done by Balasubramaniam et al where 88% of the individuals had bilateral representation which is also similar to the study done by Querishi et al where 74% patients had bilateral presentation.[24,26] This proves that the disease is almost bilateral.

Sandhu et al conducted a study on 131 eyes of 118 patients. The main diagnoses on FFA were 56 CNVs with a classic component and 25 occult CNVs.[27] Three serous PEDs, 26 eyes with drusen/atrophy, and 21 other diagnoses: normal (six), RVO (three), cystoid macular oedema (CMO) (two), ERM (two).

In our study in FFA out of classic CNVM, 29 (25.4%) in were pure classic, 23 (20.2%) had predominant CNVM and 11 (9.6%) minimal CNVM. Late leak occult CNVM was observed in 17 (14.9%), RAP in 1 (0.9%), serous PED in 2 (1.8%). Drusen in patients with no CNVM in 13 (11.4%) and atrophy in 4 (3.5%) eyes. On OCT classic CNVM was seen in 65 (57%) eyes, occult CNVM in 19 (16.7%) eyes, serous PED in 21 (18.4%) eyes, no CNVM (drusen/atrophy/cataract) in 9 (7.9%) eyes. There was no view on OCT in 3 patients with cataract.

In our study, OCT showed sensitivity of 79.1% (95% confidence interval (CI): 67.3-90.7) and specificity 84.3% (95% CI: 74.5-92.9), with positive and negative predictive values 78.7% and 85.4%, respectively, (95% CI: 65.5-95.6) and (74.8-93.4]. Similar results were obtained by Mathew et al where SDOCT showed high sensitivity (85.7-98.3%) and specificity (84.2-100%).[28] The study done by Nikolopoulou et al reported that OCTA had sensitivity of 88% and specificity of 90%.[29] Another study by Shaimov et al reported sensitivity and specificity of OCTA to be 89.2% and 93.3%, respectively.[30] These results were also consistent with our study.

There are few limitations to our study. The sample size being one of them and the auto-focus of SD-OCT needed manual adjustments in some cases.

CONCLUSION

Though, FFA is the gold standard procedure for screening ARMD and detection of dry ARMD, but OCT is more specific diagnostic tool in detecting early subretinal neovascular membrane and also to assess the extent, location and activity of the neovascular membranes. It is concluded that SD-OCT is highly sensitive for identifying AMD, CNV, and CNV activity and due to its non-invasive nature with no adverse effects and less time consuming can be used as a first line of

diagnostic modality and FFA be reserved for cases where SD-OCT is not helpful.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Tso MO. Pathogenetic factors of aging macular degeneration. Ophthalmology. 1985;92:628-35.
2. Handelman GJ, Dratz EA. The role of antioxidants in the retina and retinal pigment epithelium and the nature of prooxidant-induced damage. Adv Free Radic Biol Med. 1980;2: l-9.
3. Bray TM, Bettger WJ. The physiological role of zinc as an antioxidant. Free Radic Biol Med. 1990;8:281-91.
4. Krinsky NI. Antioxidant functions of carotenoids. Free Radic Biol Med. 1989;7:617-35.
5. Hyman LG, Lillienfeld AM, Ferris III FL, Fine SL. Senile macular degeneration: a case-control study. Am J Epidemiol. 1983;118:213-27.
6. Chandra SR, Gragoudas ES, Friedman E, van Buskirk CM, Klien ML. Natural history of disciform degeneration of the macula. Am J Ophthalmol 1974;78:579-82.
7. Gregor Z, Bird AC, Chisholm IH. Senile disciform macular degeneration in the second eye. Br J Ophthalmol. 1977;61:141-7.
8. Strahlman ER, Fine SL, Hills A. The second eye of patients with senile macular degeneration. Arch Ophthalmol 1983;101:1191-93.
9. Macular Photocoagulation Study Group. Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. Arch Ophthalmol. 1993;111:1189-99.
10. Reddy U, Krzystolik M. Antiangiogenic therapy with interferon alfa for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2006;1:CD005138.
11. Macular Photocoagulation Study Group. Sub foveal neovascular lesions in age-related macular degeneration. Arch Ophthalmol. 1991;109:1242-57.
12. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin. One-year results of 2 randomized clinical trials-TAP Report 1. Arch Ophthalmol. 1999;117:1329-45.
13. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of sub foveal choroidal neo vascularization in age-related macular degeneration with verteporfin. Two-year results of 2 randomized clinical trials-TAP Report 2. Arch Ophthalmol. 2001;119:198-207.
14. Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of sub foveal choroidal neo vascularization in pathological myopia with verteporfin: one-year results of a randomized clinical trial-VIP Report Number 1. Ophthalmology. 2001;108:841-52.
15. Verteporfin in Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of sub foveal choroidal neo vascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization-VIP Report Number 2. Am J Ophthalmology. 2001;131:541-60.
16. Hee MR, Baumal CR, Puliafito CA. Optical coherence tomography of age-related macular degeneration and choroidal neovascularisation. Ophthalmology. 1996;103:1260-70.
17. Rogers AH, Martidis A, Greenberg PB. Optical coherence tomography findings following photodynamic therapy of choroidal neovascularisation. Am J Ophthalmol. 2002;134:566-76.
18. Hee MR, Izatt JA, Swanson EA. Optical coherence tomography of the human retina. Arch Ophthalmol. 1995;113:325-32.
19. Schuman JS, Puliafito CA, Fujimoto JG. Age-related macular degeneration. in optical coherence tomography of ocular diseases. 2nd ed. New York: Slack Incorporated. 2004;243-344.
20. El-Sadany AEI, Marey HM, El-Sawy MF, Fadel AZ. Correlation of optical coherence tomography and fluorescein angiography imaging in neovascular age-related macular degeneration. Menoufia Med J. 2015;28:902-7.
21. Chhablani J, Deepa MJ, Tyagi M, Narayanan R, Kozak I. Fluorescein angiography and optical coherence tomography in myopic choroidal neovascularization. Eye (London). 2015;29(4):519-24.
22. Bressler NM, Bressler SB, West SK. The grading and prevalence of macular degeneration in Chesapeake Bay Watermen. Arch Ophthalmol. 1989;107:847-52.
23. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992;99:933-43.
24. Balasubramaniam P, Elumalai S. Comparison of fundus fluorescein angiography and optical coherence tomography in age-related macular degeneration. JEBMH 2016; 3(84): 4570-76.
25. Ryan SJ, Schachat AP, Wilkinson CP. Age-related macular degeneration. In: Text book of retina. 5th edn. Vol 2. Elsevier. 2005;907-1012.
26. Qureshi T, MajidNazir, Abdulla N. Profile of age-related macular degeneration in a Kashmiri population- a hospital-based study in tertiary care hospital in Kashmir, India. GJMEDPH. 2013;2(2):1-7.
27. Sandhu SS, Talks SJ. Correlation of optical coherence tomography with or without additional

colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. Brit J Ophthalmol. 2005;89(9):967-70.
28. Mathew R, Pefkianaki M, Kopsachilis N, Brar M, Richardson M, Sivaprasad S. Correlation of fundus fluorescein angiography and spectral-domain optical coherence tomography in identification of membrane subtypes in neovascular age-related macular degeneration. Ophthalmologica. 2014;231:153-9.
29. Nikolopoulou E, Lorusso M, Micelli Ferrari L, Cicinelli MV, Bandello F, Querques G et al. Optical coherence tomography angiography versus dye angiography in age-related macular degeneration: sensitivity and specificity analysis. BioMed Res Int. 2018;2018:7.
30. Shaimov TB, Panova IE, Shaimov RB, Shaimova VA, Shaimova TA, Fomin AV. Optical coherence tomography angiography in the diagnosis of neovascular age-related macular degeneration. Vestn Oftalmol. 2015;131:4-12.

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