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A DESCRIPTIVE LONGITUDINAL STUDY OF CHANGES IN THE MEASUREMENT OF MACULAR THICKNESS AFTER USING INTRAVITREAL BEVACIZUMAB IN AGE RELATED MACULAR DEGENERATION BY USING OPTICAL COHERENCE TOMOGRAPHY

Ophthalmology

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ABSTRACT

BACKGROUND: Age related macular degeneration (ARMD) affects the elderly population and is a serious cause of irreversible blindness in its advanced forms. ARMD may be of dry or wet types. Advanced dry form consists of geographic atrophy over the macula which is untreatable. The wet type involves the formation of a choroidal neovascular membrane over the macula. The wet type may be reversible with appropriate use of anti-VEGF agents. Optical Coherence Tomography (OCT) is a non-invasive tool which can be used to measure macular thickness, assess the severity and monitor the progress of this disease.

METHOD: A hospital based descriptive, longitudinal study was conducted with 50 patients to evaluate changes in measurement of macular thickness after using intravitreal bevacizumab in age related macular degeneration by using optical coherence tomography.

RESULTS: There was significant decrease in central retinal thickness (CRT) values from baseline (412.06±2.31µm) to post 7 days (344.47±1.37µm) and 3 months (229.38±1.39µm) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).
There was significant increase in BCVA log MAR values from baseline (0.79±0.07) to post 7 days (0.71±0.06) and 3 months (0.64±0.09) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).

CONCLUSION: Intravitreal bevacizumab injection can improve visual acuity in patients with age related macular degeneration. There was a significant reduction of Central Retinal Thickness post 7 days and 3 months of intravitreal injection Bevacizumab.

KEYWORDS

Age related macular degeneration, Optical Coherence tomography, Central Retinal thickness, choroidal neovascular membrane, Anti-VEGF.

INTRODUCTION

Age-related macular degeneration (ARMD) is one of the leading causes of severe visual deficit and blindness worldwide. Its incidence at ages between 65 and 75 years ranges from 9 to 25%. It may lead to blindness in over 80% of affected patients, above 70 years of age. In people over 85 years, the risk of developing advanced ARMD lesions is ten times compared with 70–74 years old people.[1] ARMD is estimated to be responsible for 26% of cases of blindness, followed by glaucoma (20.5%) and diabetic retinopathy (8.9%).[2] The beaver dam offspring study (BOSS), was conducted on 2810 subjects. The ages were between 21–84 years. It revealed that the incidence of early ARMD ranges from 2.4% among people 21–34 years of age to 9.8% in people over 65 years of age.[1] In this study, the incidence of early and advanced forms of ARMD was estimated at 14.3% and 3.1%, respectively, among 3917 participants from 43 to 86 years old, increasing with age. The risk of developing advanced ARMD lesions in one eye of patients who already had one-eye lesions was reduced to 43% in the study of age-related eye diseases study (AREDS).[3] The risk of progression to advanced ARMD in patients who suffered from early bilateral or unilateral lesions was assessed at 26.4% and 6.3% respectively.

Classification

Early ARMD: Defined by the presence of numerous small (<63 microns, "hard") or intermediate (≥63 microns but <125 microns, "soft") drusen.

Small drusen can represent an epiphenomenon of aging and are frequently seen in those 50 and older, (therefore, intermediate drusen are more specific for ARMD).[4,5]

Intermediate ARMD: Macular disease characterized by either extensive drusen of small or intermediate size, or any drusen of large size (≥125 microns). 124 micron is the average diameter of retinal vein at the optic disc margin.

Advanced ARMD: Defined by the presence of either geographic atrophy or choroidal neovascular membrane (along with its sequelae, such as subretinal or sub- RPE hemorrhage or serous fluid, and subretinal fibrosis).[6]

The use of anti-vascular endothelial growth factor (anti-VEGF) agents is very common in the general treatment of neovascular-Age Related macular degeneration (AMD).[7,8]

Bevacizumab is a full.length antibody with properties similar to those of ranibizumab. It is approved for systemic use in some solid tumours.[9] Intravitreal injections of bevacizumab are currently being used to treat various neovascular and exudative diseases.

Sizmaz S et al study[10] reported that the Intravitreal injection of bevacizumab provided a significant reduction in Central Retinal Thickness.

Sizmaz S et al[10] in 2014 found that mean central retinal thickness (CRT) showed significant decrease after single injection of ranibizumab (from 345.0 µm to 253.5 µm, p<0.01) and bevacizumab (from 329.5 µm to 251.0 µm, p<0.01) at the first month, respectively.

Rosenfeld PJ et al[11] in 2016 concluded that Optical coherence tomography imaging was adopted as a method to detect excess VEGF. It has evolved to become the gold standard imaging strategy for diagnosing neovascular AMD, evaluating disease progression, assessing treatment responses to drugs and deciding when to re-treat.

de Almeida NA et al[12] in 2018 concluded that Intravitreal injection of ranibizumab, can produce changes early, in optical coherence tomography parameters. There is also an improvement in perceived quality of vision of patients with sub-foveal exudative age-related macular degeneration.

Karthikeyan Radhamma LP et al[13] in 2019 concluded that there was significant increase in BCVA following intravitreal bevacizumab injection in wet AMD. After repeated injections higher improvement was noted.

MATERIAL AND METHODS

Study design: A hospital based descriptive, longitudinal study

Study Duration: 18 months

Study area: The study was done at our tertiary care centre in the department of Ophthalmology on attending OPD/IPD.

Study population: All patients visiting ophthalmology OPD/ eye camp diagnosed with exudative age related macular degeneration i.e. presence of choroidal neovascularization on direct, indirect ophthalmoscopy or on optical coherence tomography at our Tertiary care Hospital who fulfilled the inclusion criteria.

Sample size: 50 patients

Sample size was calculated using the formula:
$n = [z^2 p(1-p)]/d^2$

Where: Z = table value of alpha error from Standard Normal Distribution table (0.95) Power (p) = 80%

Precision error of estimation (d) = 5.5%
n= [0.95 x 0.95 x 0.8 (0.2)] / 0.055 x 0.055 = 47.7

Hence a sample size of 50 patients was considered adequate for our study.

INCLUSION CRITERIA

- All patients visiting ophthalmology OPD/ eye camp diagnosed with exudative age-related macular degeneration i.e. presence of choroidal neovascularization on direct, indirect ophthalmoscopy or on optical coherence tomography.
- Patients of both sexes.
- Age more than 18 years willing to participate in the study.

EXCLUSION CRITERIA:

- Pregnant and critically ill patients
- Patients with history of intra vitreal injections, laser therapy and ocular surgeries.
- Patients with other ocular diseases
- Patients with history of ocular trauma.
- Patients with history of allergy to bevacizumab
- Patients not willing to participate in the study

METHODOLOGY

The study was done in patients with diagnosed exudative Age related macular degeneration admitted in the Ophthalmology ward in the hospital and given injection bevacizumab during the study period. Written consent of all patients included in the study were taken after fully explaining the procedure and purpose of study to patients.

In our set up, patients diagnosed with age related macular degeneration were managed in the following way:

A complete ophthalmic history was taken. A comprehensive clinical examination was done including

1. Snellen and logMAR Visual Acuity measurement
2. External Examination under torch light
3. Examination of the posterior segment by ophthalmoscopy (direct and indirect) and +90D biomicroscopy
4. Intraocular pressure measurement using Applanation Tonometer
5. Pachymetry
6. Fundus Photography
7. Routine systemic examination
8. Fundus fluorescein angiography
9. Optical coherence tomography

After taking history for any eye symptoms, anterior segment was examined with torch light and slit lamp. Both pupils were then dilated with 1% tropicamide + 0.5% phenylephrine eye drops and fundus examination was done by ophthalmologist with direct ophthalmo scope in a semi dark room in the ward. Exudative Age related macular degeneration changes (choroidal neovascularization) was taken as positive finding in that patient. Following this a baseline optical coherence tomography was noted. Then the patient was given intravitreal bevacizumab in the operation theatre by consultant ophthalmologists.

The patients were asked to follow up after 7 days and 3 months of intravitreal injection bevacizumab and examined.

The patient details like their name, age, sex, address and co morbid conditions like diabetes, hypertension etc. were taken from medical records. Their pre and post injection OCT findings were recorded and macular thickness were compared.

OBSERVATIONS AND RESULTS

A hospital based descriptive, longitudinal study was conducted with 50 patients to evaluate changes in measurement of macular thickness after using intravitreal bevacizumab in age related macular degeneration by using optical coherence tomography.

Baseline Parameters of patients

The baseline central retinal thickness (CRT) values was 412.06±2.31µm and Best Corrected Visual Acuity (BCVA) log MAR values was 0.79±0.07.

Table 1: Baseline Parameters of patients

Baseline Parameters	Mean	SD
CRT (µm)	412.06	2.31
BCVA	0.79	0.07

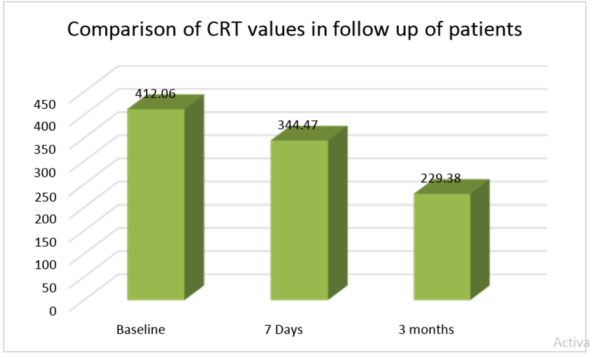
CRT - Central Retinal Thickness; BCVA – Best Corrected Visual Acuity

Comparison of Central Retinal Thickness (CRT) values in follow up of patients

There was significant decrease in central retinal thickness (CRT) values from baseline (412.06±2.31µm) to post 7 days (344.47± 1.37µm) and 3 months (229.38±1.39µm) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).

Table 2: Comparison of CRT values in follow up of patients

CRT (µm)	Baseline		7 Days		3 months		p Value
	Mean	SD	Mean	SD	Mean	SD	
	412.06	2.31	344.47	1.37	229.38	1.39	**<0.05**

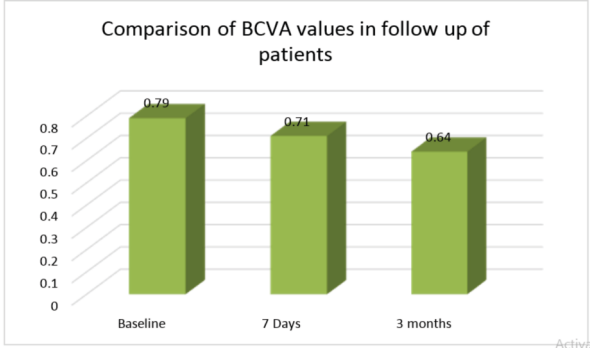


Graph 1: Comparison of CRT values in follow up of patientsComparison of Best Corrected Visual Acuity (BCVA) values in follow up of patients

There was significant increase in BCVA log MAR values from baseline (0.79±0.07) to post 7 days (0.71±0.06) and 3 months (0.64±0.09) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).

Table 3: Comparison of BCVA values in follow up of patients

	Baseline		7 Days		3 months		p Value
	Mean	SD	Mean	SD	Mean	SD	
BCVA	0.79	0.07	0.71	0.06	0.64	0.09	**<0.05**



Graph 2: Comparison of BCVA values in follow up of patients

DISCUSSION

In this study, there was significant decrease in central retinal thickness (CRT) values from baseline (412.06±2.31µm) to post 7 days (344.47±1.37µm) and 3 months (229.38±1.39µm) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**). This is comparable to the studies of de Almeida NA et al[12], Karthikeyan Radhamma LP et al[13] and Sizmaz S et al[10]

de Almeida NA et al[12] interventional, non-randomized, open label prospective study observed retinal thickness values started at 524.5 µm and decrease to 353.0 µm on day 30.

Karthikeyan Radhamma LP et al[13] retrospective cohort study showed mean Central Foveal Thickness (CFT) values reduced after intra-vitreal Avastin (IVA). The mean CFT before IVA was 417 µm. After the first dose the mean CFT has reduced to 343 µm. Further reduction was observed after second and third dose of IVA (mean CFT after 2nd dose = 330.08 µm and mean CFT after 3rd dose = 307.92 µm respectively).

In the present study, there was significant increase in BCVA log MAR values from baseline (0.79±0.07) to post 7 days (0.71±0.06) and 3 months (0.64±0.09) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**). This in concordance to the studies of de Almeida NA et al[12], Novais EA et al[14], Michael SW[15] and Karthikeyan Radhamma LP et al[13].

de Almeida NA et al[12] interventional, non-randomized, open label prospective study showed comparison with the baseline values (0.81±0.16) showed a gradual increase in BCVA observed after ranibizumab intravitreal injection (0.72 ± 0.23 at day 7), becoming even more evident after 30 days (0.67 ± 0.24) with statistically significant difference.

Karthikeyan Radhamma LP et al[13] retrospective cohort study found mean BCVA (log MAR) after first dose, improved to 1.262±0.502. The mean BCVA (log MAR) after second dose is found to be 1.17±0.542. The mean BCVA (log MAR) after third dose is 1.084±0.508 showed statistically significant difference and good improvement in visual acuity.

In our study, visual acuity in patients with AMD from baseline after the first intravitreal injection of bevacizumab demonstrated a statistically significant difference over 3 months, which may be verified by the reduced values of the retinal thickness. Similar observations were noted in the studies of Desai NK et al[16], Iqbal K et al[17] and El Matri L et al[18].

Desai NK et al[16] study on role of intravitreal bevacizumab injection for management of neovascular age related macular degeneration carried out a study on 75 eyes of 75 patients reported Visual acuity improved to more than three lines from baseline in 21.33% patients. 64% patients had 2-3 lines gain and 6.66% patients showed 0-1- line gain in visual acuity.

CONCLUSION

1. The baseline central retinal thickness (CRT) values was 412.06±2.31µm while the intraocular pressure (IOP) and Best Corrected Visual Acuity (BCVA) logMAR values was 13.92±2.14mmHg and 0.79±0.07 respectively.
2. There was significant decrease in central retinal thickness (CRT) values from baseline (412.06±2.31µm) to post 7 days (344.47±1.37µm) and 3 months (229.38±1.39µm) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).
3. There was significant increase in BCVA log MAR values from baseline (0.79±0.07) to post 7 days (0.71±0.06) and 3 months (0.64±0.09) of bevacizumab intravitreal injection as per ANOVA test (**p<0.05**).

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