EFFECT OF INTRAVITREAL BEVACIZUMAB ON VISUAL ACUITY AND OPTICAL COHERENCE TOMOGRAPHY (OCT) CHANGES IN WET AGE-RELATED MACULAR DEGENERATION

Lekshmi Priya Karthikeyan Radhamma[1], Maria Tinu Panakal George[2], Pappa Padmavathy[3], Rajini Konayi Cherayath[4]

[1]Postgraduate, Department of Ophthalmology, Government Medical College, Thrissur, Kerala.
[2]Assistant Professor, Department of Ophthalmology, Government Medical College, Thrissur, Kerala.
[3]Associate Professor, Department of Ophthalmology, Government Medical College, Thrissur, Kerala.
[4]Professor and HOD, Department of Ophthalmology, Government Medical College, Thrissur, Kerala.

ABSTRACT

BACKGROUND

Age-related Macular Degeneration (AMD) is the leading cause of blindness in patients over the age of 60 years. AMD associated with vision loss are divided into Atrophic (Dry) type and Neovascular (Wet) type. Intravitreal anti-vascular endothelial growth factor agents are used in the treatment of choroidal neovascularisation secondary to Wet AMD. This study was done to evaluate the improvement in visual acuity and OCT changes in Wet AMD after the intravitreal injection of bevacizumab (Avastin).

METHODS

Retrospective cohort study was conducted on a total of 50 eyes of 50 patients. Informed consent was taken. Detailed ocular examination was done. Spectral Domain OCT was carried out to diagnose and monitor the improvement of choroidal neovascularisation and sub retinal fluid (SRF). Data was analysed using SPSS 21.0 version software.

RESULTS

Majority of the patients (48%) belongs to 61-70 age category. 56% were male patients. Amsler Grid showed that 18 patients had metamorphopsia and 20 had positive scotoma. An average of 3.24 doses of intravitreal Avastin (IVA) were given to the patients. The mean best corrected visual acuity (BCVA) in log MAR value before IVA is 1.356 (SD =0.508). Improvement was found to be 1.262 (SD = 0.502) after first dose, 1.17 (SD = 0.542) after second dose and 1.084 (SD = 0.508) after third dose. The mean central foveal thickness (CFT) before IVA was 417 µm. After the first dose, the mean CFT reduced to 343 µm. Further reduction was observed after repeated injections (330.08 µm after second and 307.92 µm after third respectively).

CONCLUSIONS

There was significant increase in BCVA following intravitreal bevacizumab injection in wet AMD. More improvement was noted after repeated injections. There was a significant reduction in SRF and CFT in OCT after IVA injections. However, intra ocular pressure (IOP) was found to increase significantly after IVA.

KEYWORDS

Intravitreal Bevacizumab, Visual Acuity, Optical Coherence Tomography, Wet Age-Related Macular Degeneration

HOW TO CITE THIS ARTICLE: Lekshmi Priya KR, Maria Tinu PG, Padmavathi P, et al. Effect of intravitreal bevacizumab on visual acuity and optical coherence tomography (OCT) changes in wet age-related macular degeneration. J. Evid. Based Med. Healthc. 2019; 6(34), 2286-2289. DOI: 10.18410/jebmh/2019/467

BACKGROUND

Age related macular degeneration (AMD) is a degenerative disorder causing irreversible blindness in patients over the age of 60 years. The disease has a profound effect on quality of life of the affected individuals. Due to the exponential increase in life expectancy, it represents a major socioeconomic challenge. It has been estimated that by 2050, 25% Asians will be over 60 years. This indicates that, there will be a large increase in AMD over next few decades and would create large economic burden.[1] In India, the percentage of prevalence varies from 0.6% to 2.7% in South India and 0.6% to 4.7% in North India.[2] AMD is classified into two types – Dry (non-neovascular or atrophic) and Wet (neovascular or exudative). Dry AMD is the most common form comprising of 90% of diagnosed cases. Neovascular AMD includes choroidal neovascularisation (CNV) and its associated manifestations such as retinal pigment epithelial detachments (PED), fibrovascular disciform scarring, vitreous haemorrhages and retinal pigment epithelial tears. CNV is associated with abnormal growth of blood vessel complex from the choriocapillaris through the breaks in Bruch membrane. Various growth factors are suspected in the development of CNV such as vascular endothelial growth factor (VEGF) which binds to endothelial cell receptors promoting angiogenesis and vascular leakage.[3] Intravitreal anti- VEGF agents such as Bevacizumab (Avastin) prevent VEGF-A form of the cytokine interacting with the relevant receptors on the endothelial cell surface and hence retard or reverse CNV.[4]

Financial or Other, Competing Interest: None.
Submission 02-08-2019, Peer Review 05-08-2019,
Acceptance 21-08-2019, Published 23-08-2019.
Corresponding Author:
Dr. Maria Tinu P. G,
Panakal House, Kumbalanghi P. O.,
Cochin- 682007, Kerala.
E-mail: mariatinu@gmail.com
DOI: 10.18410/jebmh/2019/467

Bevacizumab is a larger complete antibody which is retained in the vitreous for a longer period and hence may be given less frequently. The dose of Bevacizumab is usually 1.25 mg/ 0.05 ml or 2.5 mg/0.1 ml. Previous studies have shown improvement in visual acuity and optical coherence tomography (OCT) changes due to intravitreal Avastin (IVA). IVA is a safe and effective drug in treatment of neovascular AMD in terms of improvement in best corrected visual acuity (BCVA) and reduction in central foveal thickness (CFT) on OCT without any adverse effects. In Wet AMD, OCT can be used to identify the presence of intraretinal or subretinal fluid (SRF) and presence of PEDs. In OCT, typically CNV is shown as thickening and fragmentation of retinal pigment epithelium-choriocapillaris high reflectivity band. The major use of OCT in the management of CNV is in monitoring the response to treatment, for which it provides an accurate quantitative assessment.

We wanted to study the effect of intravitreal Bevacizumab on visual acuity in Wet Age Related Macular Degeneration (AMD). We also wanted to study the changes in Optical Coherence Tomography (OCT) of Wet AMD after the intravitreal injection of Bevacizumab.

METHODS

The study was conducted at Department of Ophthalmology, Government Medical College, Thrissur for a period of one year. Prior to commencement, the study was approved by the ethical committee of the medical college.

Study Design

Retrospective Cohort Study.

Study Participants

Patients of Wet AMD who were treated with three or more doses of intravitreal injection of Bevacizumab, in Department of Ophthalmology, Government Medical College, Thrissur.

Sample Size

Sample size is calculated using the formula "4 pq/d2",

where-

p = proportion of visual outcome, 78% (from the study by Damir et al.)[5]

q = 100-p

d= allowable error is 10% of p with power of 90%

Calculated sample size is 112. However according to previous data, number of patients taking IVA in wet AMD in one year period is only 50 in our Department. So all the detected cases of Wet AMD who have taken 3 or more doses of IVA injections were included in the study.

Inclusion Criteria

1. Ability and willingness to provide informed consent irrespective of age and gender.
2. Patient diagnosed as Wet AMD clinically and suspected cases of Occult CNV confirmed by using Fundus Fluorescein angiography and who have taken 3 or more doses of IVA injections

Exclusion Criteria

1. Patients with other macular diseases such as diabetic maculopathy, central serous chorio retinopathy (CSCR), infective choroiditis, venous occlusion, macular choroiditis and idiopathic polypoidal choroidal vasculopathy (IPCV).
2. Patients who have already taken injections from other hospitals for Wet AMD.
3. Patient with CNV following trauma, Myopic CNVM etc.,
4. Patients with systemic contra indications for IVA like CAD, Stroke, Thromboembolic disorders etc.

Study Tools

Snellen's chart, Optical Coherence Tomography (OCT), Fundus Fluorescein Angiography (FFA).

A prepared dose of 1.25 mg (0.05 ml) injection in a 26G insulin syringe was given for each patient from commercially available 4 ml vial of bevacizumab (25 mg/ml) using aseptic techniques. The eyes to be treated were prepared with 5% povidone iodine solution. Topical anaesthesia was administered using proparacaine hydrochloride 1% ophthalmic drops. The site of injection was measured with the help of a calliper. Using a 26G needle, 0.05 ml of Avastin was injected intravitreal through the pars plana about 3.5 mm to 4 mm from the limbus. Three baseline doses of intravitreal injection of Avastin was given in an interval of six to eight weeks and if there was no improvement in OCT, repeated injections of IVA were given and OCT changes were monitored. After the injection, patients were instructed to use topical Moxifloxacin 0.5% four times a day and timolol eye drops two times a day for one week. Patients were examined at one week and four weeks after each injection. At each visit, BCVA was measured along with the slit lamp examination of the anterior segment, measurement of intraocular pressure and dilated fundus examination. OCT was taken after four weeks of bevacizumab injection and to monitor the reduction in CFT, choroidal neovascularisation and SRF. This is the department protocol for administration of IVA in Wet AMD patients. Data for study was collected from records of patients retrospectively

Ethical Clearance

Study proposal was cleared by institutional research board prior to the beginning of data collection. Expense of the study was met by principal researcher. There was no conflict of interest involved.

Data Analysis

Data collected from each individual was entered into an Excel sheet. The coding of the variables and appropriate analysis was done with the help of SPSS 21.0 version.

RESULTS

BCVA	6/6 (0)*	6/9 (0.2)*	6/12 (0.3)*	6/18 (0.5)*	6/24 (0.6)*	6/36 (0.8)*	6/60 (1.0)*	5/60 (1.1)*	4/60 (1.2)*	3/60 (1.3)*	2/60 (1.5)*	1/60 (1.8)*	<1/60 (2.0)*
BCVA Before IVA	0	0	2	1	1	5	8	4	3	4	3	8	11
After 1st dose of IVA	0	2	2	1	1	3	9	3	6	4	5	8	6
2nd dose of IVA	0	2	1	3	3	11	5	3	2	2	4	8	6
3rd dose of IVA	0	2	2	3	3	7	9	4	2	1	6	5	4

Table 1. Best Corrected Visual Acuity (BCVA)- Before & After IVA

*Log MAR values

IVA	Improved	Stable	Decreased	Total
After 1st Dose	25(50%)	18(36%)	7(14%)	50
2nd Dose	36(72%)	6(12%)	8(16%)	50
3rd Dose	39(78%)	7(14%)	4(8%)	50
Last Dose	39(78%)	7(14%)	4(8%)	50

Table 2. Visual Acuity after IVA

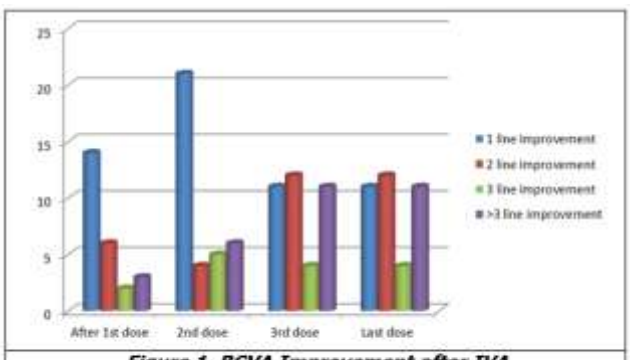

Figure 1. BCVA Improvement after IVA

After first dose 14 patients had one-line improvement whereas 3 patients had more than three-line improvement. After the last dose, 11 patients showed significant improvement of more than three line.

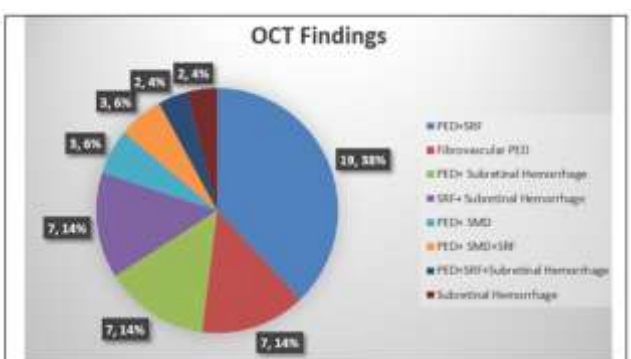

Figure 2. OCT Findings before IVA

*PED- Pigment epithelial detachment, *SRF- Sub retinal fluid, *SMD- Sub macular detachment

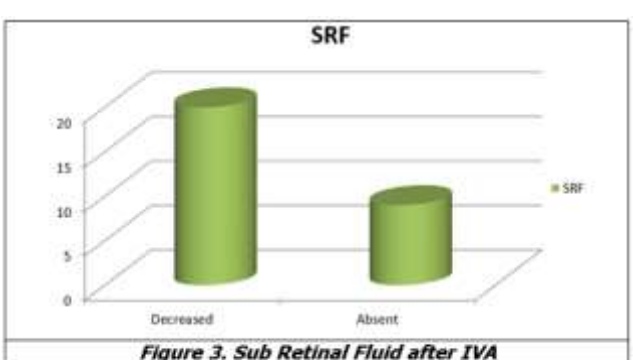

Figure 3. Sub Retinal Fluid after IVA

20 patients had decreased subretinal fluid after IVA where as in 9 patients it was absent.

CFT	<250µ	250-350µ	351-450µ	451-550µ	551-650µ	>650µ
Before IVA	0	17	14	13	5	1
After 1st dose	11	20	13	4	2	0
2nd dose	12	22	12	3	1	0
3rd dose	14	26	9	1	0	0

Table 3. CFT Before and After IVA

IOP	<10 mmHg	10 mmHg	12 mmHg	14 mmHg	16 mmHg	18 mmHg	20 mmHg	>21 mmHg
Before IVA	1	8	12	16	9	3	1	0
After 1st dose	0	5	13	18	6	2	2	4
2nd dose	0	4	11	17	7	4	4	3
3rd dose	0	4	12	16	8	3	4	3

Table 4. Intraocular Pressure before and after IVA

DISCUSSION

The mean BCVA (log MAR) after first dose, improved to 1.262 (SD = 0.502). The mean BCVA (log MAR) after second dose is found to be 1.17 (SD = 0.542). The mean BCVA (log MAR) after third dose is 1.084 (SD = 0.508) which shows good improvement in visual acuity. The t-values and p-values of BCVA and IVA after first, second and third dose (t-value = 5.779 (p-value <0.05); t-value = 11.884 (p-value <0.05); t-value = 12.494 (p-value <0.05)) showed statistically significant difference. Similar reports were observed in previous studies as well. Desai et al., carried out a study on 75 eyes of 75 patients. Visual acuity got 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.[6] Iqbal et al., reported that the mean VA improved from 0.21±0.11 before injections to 0.43±0.11 after injections at six months.[7] The researchers found out that IVA is effective in improving and stabilizing the visual acuity in patients with neovascular AMD(Mahar and Hanfi).[8] Ehrlich et al., studied the effect of IVA for the treatment of long standing exudative age related macular degeneration and low visual acuity. The results showed that Snellen visual acuity improved.[9] Galbinur et al., studied the efficacy of intravitreal bevacizumab injections for eyes with neovascular age related macular degeneration and poor initial visual acuity. Patients received a mean of 2.6 IVA and mean visual acuity improved from 1.85 to 1.52 Log MAR.[10] Matri L et al., evaluated functional and anatomic effects of IVA in patients with neovascular AMD and initial low visual acuity. It was concluded that IVA injection may increase the chance of visual acuity gain in neovascular AMD even in cases with initial low visual acuity.[11] Michels et al., reported on systemic Avastin for the treatment of neovascular AMD in nine patients followed over three months and this cohort was subsequently expanded to eighteen patients followed over six months. During these 6 months, the authors

observed a rapid and sustained improvement in visual acuity and anatomical outcomes.[12]

Yoganathan et al., studied the visual and anatomic outcome of IVA in the treatment of exudative age-related macular degeneration (AMD). Mean visual acuity increased by 6.5 letters (P-0.01) at 4 weeks and 5.3 letters (P-0.01) at 24 weeks after initial injection.[13] Azad et al., (2008) investigated the 6 month safety profile and clinical outcomes of IVA for treating subfoveal CNV secondary to AMD in Indian population.[14] At the end of six month follow up, mean BCVA improved from 20/160 to 20/100.

The mean CFT values have reduced after 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). The t-values with corresponding p-values show that the reduction in CFT values after IVA is statistically significant since p-values are less than the cut-off 0.05 (t-value = 14.309 ($p<0.05$), t-value = 12.3 ($p<0.05$), t-value = 12.05 ($p<0.05$)). Desai et al., showed that 80% patients had decrease in CFT of more than 100 microns from baseline at the end of one year.[6] Ehrlich et al., showed decrease in mean CFT.[9] The mean IOP before IVA is 13.48 (SD = 2.54). The mean IOP after first dose of IVA has increased to 14.36 (SD = 3.225). The mean IOP after second dose of IVA has increased to 14.80 (SD = 3.207). The mean IOP after third dose is 14.72 (SD = 3.201). There was a significant increase in the IOP after IVA doses. Falkenstein et al., reported that three minutes post injection the IOP had risen and then fell down spontaneously at ten minutes.[15] The researchers reported that Avastin injections caused a predictable probably volume related rise in IOP and which spontaneously fell to below 30 mmHg in all eyes within 15 minutes.

Limitations

The study was carried out with a small number of subjects. Hence, study with larger sample size is recommended as it will provide more statistically significant results thus making the findings more concrete. The patients in the study may still require further bevacizumab injections and may not have exhibited their final visual acuity.

CONCLUSIONS

Intravitreal Bevacizumab injection resulted in significant improvement in Best Corrected Visual Acuity in wet AMD. The visual acuity after the third dose was higher when compared to the second and first doses respectively. The subretinal fluid in OCT was significantly reduced after IVA injection. There was a significant decrease in CFT following IVA. As the number of doses of IVA increased from first to the third, there was a significant reduction of CFT and SRF. The Intra Ocular Pressure increased significantly after IVA.

REFERENCES

[1] Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. Ophthalmology 2010;117(5):921-927.
[2] Jain IS, Prasad P, Gupta A, et al. Senile macular degeneration in northern India. Indian J Ophthalmol 1984;32(5):343-346.
[3] Adamis AP, Shima DT. The role of vascular endothelial growth factors in ocular health and disease. Retina 2005;25(2):111-118.
[4] Aggio BF, Eid Farah M, Melo GB. Intravitreal bevacizumab for occult choroidal neovascularisation with pigment epithelium detachment in age-related macular degeneration. Acta Ophthalmol Scand 2006;84(5):713-714.
[5] Damir K. Intravitreal bevacizumab for the management of age related macular degeneration. Collegium Antroplogicum 2008;32:2:5-7.
[6] Desai NK, Aggarwal SV, Negi PS, et al. Role of intravitreal bevacizumab injection for management of neovascular age related macular degeneration. Natl J Med Res 2016;6(2):130-133.
[7] Iqbal K, Baig J, Jamil H, et al. Visual results following intravitreal bevacizumab in neovascular age-related macular degeneration. Journal of the College of Physicians and Surgeons Pakistan 2011;21(9):535-538.
[8] Mahar PS, Hanfi AN. Visual outcome following intra-vitreal bevacizumab injection in neovascular age-related macular degeneration. Pak J Ophthalmol 2011;27(2):89-95.
[9] Ehrlich R, Weinberger E, Axer-Siegel R, et al. Outcome of bevacizumab (avastin) injection in patients with age related macular degeneration and low visual acuity. Retina 2008;28(9):1302-1307.
[10] Galbinur T, Averbukh E, Banin E, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration associated with poor initial visual acuity. Br J Ophthalmol 2009;93(10):1351-1352.
[11] El Matri L, Bouraoui R, Chebil A, et al. Bevacizumab Injection in Patients with age related macular degeneration associated with poor initial visual acuity. J Ophthalmol 2012;2012:1-5.
[12] Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112(6):1035-1047.
[13] Yoganathan P, Deramo VA, Lai JC, et al. Visual improvement following intravitreal bevacizumab (avastin) in exudative age-related macular degeneration. Retina 2006;26(9):994-998.
[14] Azad RV, Khan MA, Chanana B, et al. Intravitreal bevacizumab for subfoveal choroidal neovascularisation secondary to age-related macular degeneration in an Indian population. Jpn J Ophthalmol 2008;52(1):52-56.
[15] Falkenstein IA, Cheng L, Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). Retina 2007;27(8):1044-1047.