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The Efficacy of Intravitreal Bevacizumab in Neovascular Age-Related Macular Degeneration

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Objective: To study the effect of cataract surgery with intravitreal bevacizumab therapy on visual and anatomical outcomes in patients with neovascular age-related macular degeneration (AMD) in Mongolian patients. **Methods:** A retrospective analysis of 72 eyes of 36 patients with neovascular AMD evaluated intravitreal bevacizumab (1or2.5 mg) injections. Retreatment was performed following an optical coherence tomography (OCT)-based regimen. Ophthalmic examination included best-corrected visual acuity (BCVA), dilated fundus examination, and OCT image analysis. **Results:** A total of 11 patients received cataract surgery. We could not observe statistical significance between the two groups. The BCVA of the right eye of patients having cataract surgery improved by 0.21 ± 0.29, while the corresponding value for patients without surgery was 0.32 ± 0.32. The mean central retinal thickness (CRT) of patients with refraction was decreased from 264.4 ± 82.32 μm at baseline to 244.55 ± 52.59 μm for the right eye, while it was 275.4 ± 96.4 μm at baseline to 276.36 ± 68.22 μm for the left eye. **Conclusion:** Cataract surgery with intravitreal bevacizumab therapy in eyes with neovascular AMD in aged patients was performed.

Keywords: Best-Corrected Visual Acuity; Optical Coherence Tomography; Age-Related Macular Degeneration

Introduction

Age-related macular degeneration (AMD) is a retinal degenerative disease that accounts for 8.7 % of all blindness worldwide [1-3]. It has been said that the estimated population of those affected by AMD worldwide was 196 million in 2020 and is projected to increase to 288 million by 2040 [1-3]. There are two main categories of AMD: a neovascular "wet" form and a non-neovascular "dry" form. Both result in the partial or complete loss of central vision [4]. Compared to dry AMD, wet or neovascular AMD (nvAMD) accounts for almost 90% of blindness associated with AMD. The neovascular form of AMD is characterized by choroidal neovascular membrane formation and fibrosis that leads to acute visual loss [5]. Here, vascular endothelial growth factor A (VEGF-A) strongly induces vascular proliferation and migration of endothelial cells essential for both

physiological and pathological angiogenesis. In a low-oxygen environment, hypoxia cells produce transcription of the hypoxia-inducible factor 1 alpha (HIF-1 alpha) which further induces the release of VEGF-A [6-9].

The treatment of nvAMD has been developed over time. Laser photocoagulation was the earliest form of nvAMD treatment, which was targeted to destroy choroidal neovascularization (CNV). However, alone or combined with photodynamic therapy it could not improve the visual acuity in the patients [10]. On the other hand, several clinical trials confirmed anti-VEGF agents as the most relevant pharmacological strategies to improve treatment outcomes [11-14]. For example, ranibizumab is a recombinant humanized monoclonal antibody. Lowe et al demonstrated that ranibizumab was capable of binding to recombinant human VEGF165, VEGF121, and VEGF110 (KD < or = 192 pM) [15]. Another anti-VEGF agent is bevacizumab, which is a recombinant humanized anti-VEGF IgG1. A meta-analysis by Pham et al showed that the vision gain was not significantly different in patients with cn-AMD, DMO, RVO-MO, and m-CNV treated with bevacizumab versus ranibizumab [16].

Numerous studies demonstrated that AMD is the main cause of blindness in elderly patients. It has been also revealed that AMD prevalence is highly dependent on both genetic and environmental factors. A population-based cross-sectional study of 3280 Malay adults aged 40-80 years showed that, after adjusting for age, gender, smoking, hypertension, diabetes and, body mass index, participants with lower educational levels were significantly more likely to have early AMD (multivariate OR 2.2, 95 % CI 1.2 to 4.0) [17]. A Korean National Health and Nutrition Examination Survey also showed non-overweight status and higher HDL levels, generally assumed as positive health indicators, however, anemia and hepatitis B infection had a harmful associations with AMD [18, 19].

The 2013 Accelerated Study of Avoidable Blindness in Mongolia showed that age-related AMD prevalence has been estimated at 4.2 %. Investigating proper treatments, as well as developing comprehensive health strategies to prevent blindness caused by cataracts are highly demanded. Since there are not any population-based studies performed so far on age-related AMD in Mongolia, we aimed in the present study to determine the treatment regimen of nv-AMD in Mongolian patients.

Materials and Methods

Research design

We conducted a retrospective case-control study. A total of 36 participants were recruited at 2 field centers (Mongolia-Japan Hospital and Bolor Melmii Eye Hospital) in Mongolia. There were 11 patients who received cataract surgery in the case group and 25 patients in the control group. Participants in the control group did not receive cataract surgery and were matched by age with the case group. At each follow-up visit, all patients underwent best-corrected VA (BCVA) testing, intraocular pressure measurement, and biomicroscopic examination. All patients were diagnosed with nv-AMD based on FA. 14 patients received intravitreal injections of bevacizumab. Inclusion criteria for study analysis were any reduced visual acuity (VA) associated with neovascular AMD demonstrating leakage by FA as well as intra- or subretinal fluid by OCT imaging.

All injections were performed under sterile conditions in the operating room. Bevacizumab was injected into the vitreous cavity using a 30-gauge needle inserted through the inferotemporal pars plana 3.5 mm posterior to the limbus. Patients were instructed to instill one drop of topical corticoid and antibiotics (dexamethasone and gentamicin) into the injected eye after the treatment.

Data evaluation and outcome measures

The following data were collected from the medical records at baseline, at 14 days, month 1, 3 and 6 after the first injection with bevacizumab. Outcome parameters of this study included mean VA, mean 1 mm CRT, change of VA scores and OCT measurements from baseline, consecutive number of injections required to achieve a fluid-free macula, injection free interval and total number of injections received by a patient within 1 year.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD). The mean of coniferous variables for each group were checked for outliers and missing data. To compare the mean continuous variables between two groups, an unpaired t-test was carried out. Categorical variables were compared

using the Chi-square test where applicable. Multiple logistic regression was done for cataract risk factors. A P-value of 0.05 or less was considered significant. STATA version 14 software was used for statistical analyses.

Ethical statement

The study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences (No.2018/03/11). All patients provided written informed consent before participating in this study.

Results

Seventy-two eyes of 36 patients were included in the analysis. Baseline characteristics are given in Table 1. The mean age of the participants was 76 (SD 5.5) and 12 were men. The mean visual acuity of the right eye was 0.22 ± 0.28 and, the left eye was 0.23 ± 0.26. The mean pre-operative BCVA were 0.31 ± 0.30 and 0.28 ± 0.29 for the right and left eye respectively.

The cataract surgery is presented in Table 2. A total of 11 patients received cataract surgery. We could not observe statistical significance between the two groups. The BCVA of the right eye of patients having cataract surgery improved 0.21 ± 0.29, while the corresponding value for patients without surgery was 0.32 ± 0.32. However, BCVA of the left eye with surgery was 0.34 ± 0.25.

In Table 3, the mean CRT of patients with refraction decreased from 264.4 ± 82.32 μm at baseline to 244.55 ± 52.59 μm for the right eye, and it was 275.4 ± 96.4 μm at baseline to 276.36 ± 68.22 μm for the left eye.

Table 1. Baseline characteristics of patients.

Variables	Mean ±SD
Age, years	76 ± 5.5
Visual acuty right eye	0.22 ± 0.28
Visual acuty left eye	0.23 ± 0.26
BCVA right eye	0.31 ± 0.30
BCVA left eye	0.28 ± 0.29
TOD	13.8 ± 3.47
TOS	14.31 ± 3.71
CRT RE	264.4 ± 82.32
CRT LE	275.4 ± 96.4
IVAvastin right eye	3.5 ± 2.7
IVAvastin left eye	2.5 ± 1.9
Gender	N (%)
Male	12 (33.3)
Female	24 (66.7)
Cataract surgery	
Yes	11 (31.0)
No	25 (69.0)
Refraction	
Yes	14 (39.0)
No	22 (61.0)

Table 2. Cataract surgery.

Variables	Cataract Surgery			
	Case (n=11)	Control (n=25)	Total (n=36)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	78.36 ± 7.2	74.96 ± 4.47	76.0 ± 5.57	0.169
Visual acuity right eye	0.19 ± 0.28	0.24 ± 0.28	0.22 ± 0.28	0.609
Visual acuity left eye	0.27 ± 0.21	0.22 ± 0.28	0.23 ± 0.26	0.521
BCVA right eye	0.21 ± 0.29	0.32 ± 0.32	0.28 ± 0.32	0.348
BCVA left eye	0.34 ± 0.25	0.26 ± 0.31	0.28 ± 0.30	0.425
TOD	13.55 ± 4.06	13.92 ± 3.28	13.81 ± 3.48	0.791
TOS	13.64 ± 3.32	14.6 ± 3.91	14.31 ± 3.72	0.456
CRT right eye	244.55 ± 52.59	273.08 ± 92.03	264.36 ± 82.32	0.249
CRT left eye	276.36 ± 68.22	275.04 ± 107.7	275.44 ± 96.40	0.965
IV Avastin right eye	4.28 ± 1.70	3.13 ± 3.02	3.5 ± 2.68	0.268
IV Avastin left eye	3.11 ± 2.14	2.07 ± 1.75	2.45 ± 1.93	0.237
	N (%)	N (%)	N (%)	
Gender				
Male	4 (36.4)	8 (32.0)	12 (33.3)	0.832
Female	7 (63.6)	17 (68.0)	24 (66.7)	
Refraction				
Yes	5 (38.8)	9 (36.0)	14 (38.9)	0.869
No	6 (61.2)	16 (64.0)	22 (61.1)	

Table 3. Refraction.

Variables	Refrection			
	Yes (n=14)	No (n=22)	Total	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	76.0 ± 5.75	76.0 ± 5.59	76.0 ± 5.57	0.341
Visual acuty right eye	0.25 ± 0.31	0.21 ± 0.27	0.22 ± 0.28	0.658
Visual acuty left eye	0.27 ± 0.21	0.22 ± 0.28	0.23 ± 0.26	0.521
BCVA right eye	0.21 ± 0.29	0.32 ± 0.32	0.28 ± 0.32	0.348
BCVA left eye	0.34 ± 0.25	0.26 ± 0.31	0.28 ± 0.30	0.425
TOD	13.55 ± 4.06	13.92 ± 3.28	13.81 ± 3.48	0.791
TOS	13.64 ± 3.32	14.6 ± 3.91	14.31 ± 3.72	0.456
CRT right eye	244.55 ± 52.59	273.08 ± 92.03	264.36 ± 82.32	0.249
CRT left eye	276.36 ± 68.22	275.04 ± 107.7	275.44 ± 96.40	0.965
IV Avastin right eye	4.28 ± 1.70	3.13 ± 3.02	3.5 ± 2.68	0.268
IV Avastin left eye	3.11 ± 2.14	2.07 ± 1.75	2.45 ± 1.93	0.237
	N (%)	N (%)	N (%)	
Gender				
Male	8 (57.1)	4 (18.2)	12 (33.3)	0.039
Female	6 (42.9)	18 (81.8)	24 (66.7)	
Cataract surgery				
Yes	5 (35.7)	6 (27.3)	11 (30.6)	0.869
No	9 (69.3)	16 (72.7)	25 (69.4)	

Table 4. Multiple logistic regression model cataract.

Independent Variable	OR	95% CI	p-value
Age, years	1.19	0.08 - 2.34	0.119
Visual acuty right eye	1.03	0.11 - 14.11	0.451
Visual acuty left eye	1.01	0.01 - 9.41	0.627
Gender			
Male	1.00	Reference	
Female	1.10	0.42 - 1.42	0.842
Refraction			
No	1.00	Reference	
Yes	1.54	0.21 - 1.42	0.210

Discussion

Age-related macular degeneration (AMD) is a leading cause of vision loss for individuals aged more than 40 years. It has been demonstrated that patients with nv-AMD lose 3 lines of visual acuity in one year [20]. Ambati et al showed that the key mediator of the progression of AMD to late nv-AMD is vascular endothelial growth factor (VEGF) [21]. VEGF promotes angiogenesis in the initial stage of choroidal neovascularization that further leads to increased vascular permeability. Induced VEGF-A binds to the receptor and activates several signaling pathway such as the mitogen-activated protein kinase- (MAPK-) p38 signaling pathway, the phosphatidylinositol 3-kinase- (PI3K-) AKT protein kinase B pathway, and the phospholipase C gamma (PLCγ) releasing intracellular calcium, promoting prostaglandin production, and increasing vascular permeability.

Numerous studies have shown that cataract surgery leads to a significant increase in visual function quality. In the current study, we examined cataract surgery outcomes of patients with age-related nv-AMD. The mean age of our study was 76 ± 5.5. Our study found that the BCVA of the right eye of patients having cataract surgery improved 0.21 ± 0.29, while the corresponding value for patients without surgery was 0.32 ± 0.32. In the study of Jackson et al, cataract surgery in patients with retinitis pigmentosa resulted in the mean visual acuity improvement from 1.05 (SD 0.38) preoperatively to 0.63 (SD 0.49) postoperatively on the logMAR scale. Visual acuity improved in 109 eyes (77 %), was unchanged in 29 eyes (20.5 %), and worsened after surgery in four eyes (2.5 %). 86/89 patients reported major improvement of visual function [22]. Another study of retinitis pigmentosa patients also showed that, under photopic conditions, the mean BCVA improved from 0.57 to 0.31 logMAR units (P = 0.002), from 0.73 to 0.47 logMAR units with100% contrast (P = 0.029), and from 1.1 to 0.8 logMAR units with 10 % contrast (P = 0.006). Under mesopic conditions, the BCVA improved from 0.87 to 0.59 logMAR units with 100 % contrast (P = 0.02), but no significant improvement was found with 10% contrast (P = 0.18) [23]. We also observed that patients with a worse VA at baseline showed more improvement in vision through cataract surgery.

Further, in the present study, mean CRT of patients with refraction changed from 264.4 ± 82.32 μm at baseline to 244.55 ± 52.59 μm for the right eye, and 275.4 ± 96.4 μm at baseline to 276.36 ± 68.22 μm for the left eye. Moshfeghi et al presented that, CRT with the value of 342 μm and 301 μm in the laser control and IAI groups increased to 364 μm (P > 0.05 compared with last visit before surgery) and 359 μm (P = 0.013 compared with last visit before surgery), respectively [24]. A prospective study conducted on 115 yeye of 95 patients who had phacoemulsification also resulted the increased CRT from 234 ± 48 μm at baseline to 248 ± 48 μm at M1 (P = 0.005), and 252 ± 81 μm at M3 (P = 0.001) [25 - 28].

We have some limitations in the present study. Our sample size was too small thus future studies with even larger sample sizes may be needed to validate our findings. Another limitation is that the present study lacks the investigation of the longer-term macular changes and visual results. Previous studies demonstrated changes in visual acuity during the long-term investigation. Therefore, we should conduct longer-term clinical follow-up with our patients.

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