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One-Year Vision Outcomes of Age-Related Macular Degeneration in Mongolians

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Running Title: Neovascular Age-Related Macular Degeneration

Objectives: To assess the post-treatment vision outcomes in Mongolian patients with age-related macular degeneration.

Methods: Surveys assessed subjects' antioxidant intake, age, gender, race, body mass index, hypertension, smoking habits, and sunlight exposure.

Results: There were 136 cases and 100 controls, of whom 130 (55.1%) were female. Of the cases, 100 individuals had the dry type of AMD, while 36 participants had the wet type of AMD. The mean ages of the dry and wet AMD groups and controls were 75.33 ± 6.98 years, 76.0 ± 5.57 years, and 67.03 ± 7.14 years, respectively-the change of central retinal thickness and intraocular pressure by month. Our current study found that the central retinal thickness of the dry AMD group did not decrease compared to the baseline. However, the value decreased from 269.9 ± 89.17 (baseline) to 218.33 ± 41.35 at the 3-month follow-up. Concerning the intraocular pressure of all subjects, the baseline pressure of the dry AMD group was 13.88 ± 3.02, and the value was increased to 14.28 ± 2.27 after one year of treatment. In the wet AMD group, the baseline value was 14.06 ± 3.58, rising to 14.42 ± 3.51 at one-year follow-up.

Conclusion: A larger sample may produce different and better results.

Keywords: Degeneration, Macular, Age-Related, Retinal Disease, Holes

Introduction

An irreversible vision loss is commonly caused by age-related macular degeneration (AMD) in the older population. It is a significant risk factor for disability in older adults, according to approximately 9% of all cases of blindness [1-2]. Schuster et al. demonstrated that, in Germany, the number of persons with early AMD rose from 5.7 million in 2002 to 7 million in 2017-an increase of 23% in 15 years [3]. Another study also revealed that half of all cases of blindness and high-grade visual impairment in Germany are due to late-stage AMD [4]. A meta-analysis of the Chinese population showed that the crude pooled prevalence of early and late AMD among Chinese populations worldwide aged 50 years and above is 4.9% (95% CI: 3.1%-7.7%) and 0.7% (95% CI: 0.5%-1.1%), respectively [5]. In the nationwide population-based cross-sectional of the Korean population aged 40 and older, the prevalence of early- and late-AMD in the Korean population was 6.0 and 0.6%, respectively. The prevalence of early AMD increased from 1.5% in those aged 40-49 years to 16.2% in those aged ≥70 years [6].

There are two primary forms of AMD: wet and dry. Wet macular degeneration is caused by the growth of new blood vessels on the retina. On the other hand, dry macular degeneration is the most common, and it affects nearly 90 percent of seniors with AMD. Both of these types share several symptoms, such as defined spots (drusen) appearing in the central line of vision, bright colors, loss of intensity, and blurry sight of printed words [7-11]. Numerous studies reported modifiable and nonmodifiable risk factors for AMD. Blue Mountains Eye Study showed that the 5-year incidence of any late AMD lesions found in current, past, or never-smokers was 3.1%, 1.2%, and 1.4%, respectively. After adjusting for age, current smokers had an increased risk of incident geographic atrophy (RR = 3.6; 95% CI: 1.1–11.3) and any late lesions (RR = 2.5; 95% CI: 1.0–6.2) [12]. In the study of Wang et al., wet AMD was significantly associated with hypertension ($p < 0.001$). After adjustment for sex and age, the Cox regression model showed a significant association between hypertension in wet AMD patients and the number of injections (RR = 1.31, 95% CI: 1.13-1.50, $p < 0.001$) [13].

Several studies have reported the effect of cataract surgery on wet or dry AMD activity. For example, *Karisvuo* et al. examined the visual outcomes of cataract surgery of 111 patients with wet AMD. Satisfactory visual outcomes and controlled disease activity were seen in patients with wet AMD undergoing cataract surgery [14]. Another study also explored the surgery effect of wet AMD. It concluded that, despite the positive outcome on vision improvement, surgical eyes were more likely to develop new or worse cystoid changes after the study midpoint [15].
Further, numerous studies, on the other hand, demonstrated that patients who underwent cataract surgery had a higher risk of AMD progression than those who did not. The Beaver Dam Eye Study from 1988 through 1990 showed a significant association of nuclear sclerosis with early age-related maculopathy [16]. A population-based cohort of older Australians reported that the long-term (10-year) risk of developing advanced AMD in the eye undergoing surgery was significantly higher than baseline [17]. According to these studies, it is insufficient to explain the association between cataract surgery outcome and the risk of worsening AMD progression. Therefore, in the present study, we investigated possible risk factors for AMD in a representative sample of the population aged 40 years and more in Mongolia who had cataract surgery.

Materials and Methods

Research Design and Subjects

We conducted a hospital-based case-control study. Two hundred thirty-six subjects who underwent an eye checkup in a hospital were recruited for the survey. There were 136 cases and 100 controls. Age-matched controls (control group) were recruited from patients who attended the ophthalmology clinics at the same hospital. Of the cases, 100 individuals had the dry type of AMD, while 36 participants had the wet type of AMD. All patients were diagnosed with neovascular AMD based on FA, received intravitreal injections of bevacizumab, and completed at least a 6-month follow-up. Additionally, we analyzed the data of 36 patients who completed month 12 follow-up. The measurement was first repeated for one month, three months, six months, and one year.

Procedures

At each follow-up visit, all patients underwent best-corrected VA (BCVA) testing, intraocular pressure measurement, and biomicroscopic and funduscopic examination. The inclusion criteria for the study analysis were any reduced VA associated with neovascular AMD demonstrating leakage by FA and intra- or subretinal fluid by OCT imaging. Exclusion criteria were PED without angiographic evidence of CNV, advanced subfoveal fibrosis, atrophy of the RPE, or the presence of an extensive (more than 50% of the lesion involving the fovea area) submacular hemorrhage. In addition, patients who presented a history of myocardial infarction or cardiovascular event within six months before their first treatment were excluded. Follow-up and OCT criteria for retreatment Follow-up visits of all patients were performed every 6–8 weeks. Additional reinjections were given according to an OCT-guided regimen. 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 four times daily for four days after the treatment.

Data Evaluation and Outcome Measures

The following data were collected from the medical records at baseline and at months 6 and 12 after the first injection with bevacizumab: age, sex, past medical history, and the number and type of previous AMD treatments. 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 one year.

Ethical Statement

The research study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences (2018.06.22 №2018/3-11). All participants gave written informed consent.

There were 136 cases and 100 controls, of whom 130 (55.1%) were female (Table 1). Of the cases, 100 individuals had the dry type of AMD, while 36 participants had the wet type of AMD. The mean ages of the dry and wet AMD groups and controls were 75.33± 6.98 years, 76.0 ± 5.57 years, and 67.03 ± 7.14 years, respectively. Of the dry AMD patients, 73 (73%) had been diagnosed with hypertension, while 27 (75%) individuals in the wet AMD group were with hypertension. There were 68 participants (28.8%) used anticoagulant drugs.

Results

There were 136 cases and 100 controls, of whom 130 (55.1%) were female (Table 1). Of the cases, 100 individuals had the dry type of AMD, while 36 participants had the wet type of AMD. The mean ages of the dry and wet AMD groups and controls were 75.33± 6.98 years, 76.0 ± 5.57 years, and 67.03 ± 7.14 years, respectively. Of the dry AMD patients, 73 (73%) had been diagnosed with hypertension, while 27 (75%) individuals in the wet AMD group were with hypertension. There were 68 participants (28.8%) used anticoagulant drugs.

Table 1. General demographic characteristics of study participants.

Variables	Group				P-value
	Control n=100	Dry n=100	Wet n=36	Total n=236	
Age, year [a]	67.03 ± 7.14	75.33 ± 6.98	76.0 ± 5.57	71.9 ± 8.02	0.000
BMI, kg	27.04 ± 4.43	25.5 ± 4.62	26.2 ± 5.39	26.2 ± 4.70	0.062
Gender					
Male	49 (49.0)	45 (45.0)	12 (33.3)	106 (44.9)	0.071
Female	51 (51.0)	55 (55.0)	24 (66.6)	130 (55.1)	
Lens surgery					
Yes	5 (4.0)	23 (23.0)	14 (38.9)	41 (17.3)	0.051
No	95 (96.0)	78 (78.0)	22 (61.1)	196 (82.7)	
Refraction					
Yes	45 (45.0)	34 (34.0)	14 (38.9)	93 (39.4)	0.082
No	55 (55.0)	67 (67.0)	22 (61.1)	144 (60.6)	
Smoke					
Yes	22 (22.0)	32 (32.0)	7 (19.4)	61 (25.8)	0.059
No	78 (78.0)	68 (68.0)	29 (79.6)	175 (84.2)	
Hypertension					
Yes	50 (50.0)	73 (73.0)	27 (75.0)	150 (63.5)	0.089
No	50 (50.0)	25 (25.)	9 (25.0)	84 (35.5)	
Anticoagulant drug use					
Yes	22 (22.0)	33 (33.0)	13 (36.1)	68 (28.8)	0.061
No	78 (78.0)	66 (67.0)	23 (63.9)	167 (71.2)	
Sunglasses					
Yes	22 (22.0)	10 (10..0)	5 (0.08)	35 (14.8)	0.074
No	78 (78.0)	90 (90.0)	30 (99.0)	200 (84.2)	

Chi-square test, One-way ANOVA, and multiple comparisons: [a]Dry vs. Control, P-value 0.049.

Table 2 shows the vision correction by month. There was a statistically significant difference between dry and wet groups in vision first and sixth months, correction first (p=0.042) and third (p=0.041), and a year (p=0.031).

Table 2. Vision correction by month.

Variables	Study groups			
	Dry[a, b] n=100	Wet[c] n=36	Total n=372	P-value
Vision first	0.37 ± 0.26	0.23 ± 0.27	0.33 ± 0.27	0.414
Vision 1 month	0.38 ± 0.26	0.24 ± 0.27	0.34 ± 0.27	
Vision 3 month	0.37 ± 0.26	0.24 ± 0.27	0.33 ± 0.27	
Vision 6 month	0.36 ± 0.25	0.22 ± 0.26	0.32 ± 0.26	
Vision 1 year	0.35 ± 0.25	0.21 ± 0.25	0.31 ± 0.25	
Correction first	0.50 ± 0.27	0.28 ± 0.30	0.44 ± 0.31	0.042
Correction 1 month	0.49 ± 0.29	0.29 ± 0.29	0.44 ± 0.30	
Correction 3 month	0.67 ± 2.73	0.29 ± 0.30	0.60 ± 2.36	
Correction 6 month	0.55 ± 1.06	0.26 ± 0.28	0.47 ± 0.93	
Correction 1 year	0.46 ± 0.27	0.25 ± 0.28	0.40 ± 0.29	

Two-way mixed ANOVA: [a]Vision first vs. Vision 1 year, P=0.051; [b]correction first vs. Correction 1 year, P=0.045; [c]correction first vs. Correction 1 year, P=0.053

Table 3 shows the change in central retinal thickness and intraocular pressure by month. Our current study found that the central retinal thickness of the dry AMD group was decreased compared to the baseline. However, the value decreased from 269.9 ± 89.17 (baseline) to 218.33 ± 41.35 at the 3-month follow-up. About the intracortical pressure of all subjects, the baseline pressure of the dry AMD group was 13.88 ± 3.02, and the value was increased to 14.28 ± 2.27 after one year of treatment. While in the wet AMD group, the baseline value was 14.06 ± 3.58, which increased to 14.42 ± 3.51 at the 1-year follow-up.

Table 3. Central retinal thickness and Tonometer measurements by months.

Variables	Study groups			
	Dry n=100	Wet[a] n=36	Total n=372	P-value
Central retinal thickness first	218.27 ± 41.90	269.9 ± 89.17	231.9 ± 62.4	0.567
Central retinal thickness 1 month	218.35 ± 41.57	258.3 ± 163.23	228.9 ± 92.5	
Central retinal thickness 3 month	218.3 ± 41.35	218.33 ± 41.35	222.9 ± 54.3	
Central retinal thickness 6 month	218.32 ± 40.02	249.59 ± 108.18	226.6 ± 66.6	
Central retinal thickness 1 year	217.38 ± 40.40	249.14 ± 106.11	225.8 ± 65.9	
Tonometer first	13.88 ± 3.02	14.06 ± 3.58	13.9 ± 3.2	0.084
Tonometer 1 month	13.80 ± 2.57	13.83 ± 3.22	13.8 ± 2.8	
Tonometer 3 month	13.96 ± 2.58	13.67 ± 3.25	13.9 ± 2.77	
Tonometer 6 month	14.35 ± 2.29	14.14 ± 3.60	14.3 ± 2.69	
Tonometer 1 year	14.28 ± 2.27	14.42 ± 3.51	14.3 ± 2.65	

Two-way mixed ANOVA: central retinal thickness first vs. Central retinal thickness one year, P=0.050

Discussion

Age-related macular degeneration (AMD) is one of the leading causes of permanent visual loss in elderly patients. It has been demonstrated that, in 2020, among the 33.6 million blind adults over 50 years old, 1.8 million cases were found to be caused by AMD [18]. Several population-based extensive studies examined race differences in the prevalence of AMD. In the study of *Vanderbeek* et al., Latinos at age 60 had a similar hazard of developing nonexudative AMD relative to whites but had an 18% decreased hazard by age 80 ($p<0.0001$), while Asian Americans had a 28% increased hazard for developing nonexudative AMD at age 60 [19]. A systematic review by *Zhou* et al. showed that the incidence of late AMD is higher in Europe (0.26%, 95% CI 0.17% to 0.45%) than in other regions. On the other hand, the lowest incidence of early AMD occurred in Asia (1.02%, 95% CI 0.81% to 1.29%). Africans had both the highest incidence of early AMD (2.85%, 95% CI 2.46% to 3.32%) and the lowest incidence of late AMD (0%) [20].

Several treatment options for late AMD depend on the type, location, and extent of AMD. It has been suggested that anti-vascular endothelial growth factor (VEGF) therapy is the first-line treatment for neovascular AMD. The evidence from clinical trials has vastly shown the superiority of anti-VEGF to other previous treatment modalities [21-23]. For example, the phase III Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) enrolled 716 patients from 96 sites in the United States. At 24 months, 92% of patients who received 0.3 mg of ranibizumab and 90% who received 0.5 mg of ranibizumab lost fewer than 15 letters, compared with 52.9% in the sham group [21].

Further, Laser photocoagulation surgery is the first treatment used for wet AMD. During the procedure, the eye is numbed, and a high-energy laser heats, seals, and destroys abnormal leaky blood vessels. This can potentially prevent further vision loss; however, it has been said that the procedure could result in a permanent blind spot due to scarring [24-25]. In the study of *Nielsen* et al., laser treatment with blue-green argon, green argon, and krypton red was performed on 578 eyes in 443 patients with neovascular age-related macular degeneration (AMD). The short-term results showed that 16% had improved, 77% remained unchanged, and 7% had deteriorated visual acuity.

The 2013 Accelerated Study of Avoidable Blindness in Mongolia showed that age-related AMD prevalence has been estimated at 4.2 %. It is, therefore, crucial that greater attention in Mongolia be given to raising awareness of AMD and its risks not only with subjects but also with their families, who should be informed of the association between family history and AMD. In our previous study, we examined 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. Even though we could not observe statistical significance between the treatment 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.

There were, however, some limitations that may have impacted the results. Subjects were not randomly selected for participation. The sample size was also small; a larger sample size with more participating regional eye care programs would provide a broader perspective on the risk factors of AMD in Mongolia. Sunlight exposure, family history of AMD, and being older were the significant risk factors for the development and progression of AMD revealed in numerous studies in different populations. According to Schick et al.'s study, sunlight exposure during working life is significantly associated with AMD. In contrast, sunlight exposure after retirement seems to have less influence on disease development [26].

Further, in the case-control study of Argentina, the main factors of AMD were higher sunlight exposure (OR [odds ratio]: 3.3), family history of AMD (OR: 4.3) as well as hypertension (OR: 2.1), and smoking (OR: 2.2) [27]. These risk factors should have been explained in the present study. Therefore, a future study in Mongolia that uses a larger sample may produce more substantial and better results.

Conclusion

Previous studies demonstrated that patients who underwent cataract surgery had a higher risk of AMD progression than those who did not. In the present study, we investigated possible risk factors for AMD in a representative sample of the population aged 40 years and more in Mongolia who had cataract surgery. We analyzed the change in central retinal thickness and intraocular pressure by month. We revealed that the intracortical pressure of the dry AMD group was increased to 14.28 ± 2.27 after one year of treatment, while it was increased to 14.42 ± 3.51 at 1-year follow-up for wet AMD groups. Moreover, 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.

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