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ORIGINAL ARTICLE

Effects of intravitreal injection on the ocular surface and corneal endothelium in patients with neovascular age-related macular degeneration

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Abstract

Purpose: The study aimed to evaluate the effects of repeated intravitreal injection (IVI) of anti-vascular endothelial growth factors on the ocular surface and corneal endothelium in patients with neovascular age-related macular degeneration (nAMD).

Methods: This cross-sectional study included 261 nAMD patients who had undergone at least three IVIs in both eyes (Group 1), 115 patients who had recently been diagnosed with nAMD (Group 2), and 92 healthy age- and sex-matched participants (Group 3). The dry eye evaluation was performed using tear film break-up time (TBUT), the Schirmer 1 test, the Oxford scale, and the Ocular Surface Disease Index (OSDI). All groups underwent specular microscopy examination. In Group 1, the eyes received a higher number of injections were included in the study 28 days after the last IVI treatment.

Results: The mean age of the participants in Groups 1, 2, and 3 was 74.8±8.4, 73.6±9.1, and 75.1±7.4 years, respectively ($p>0.05$). In Group 1, OSDI scores were significantly higher, and TBUT and Schirmer 1 values were significantly lower than the other groups ($p<0.05$). Between groups 2 and 3, a significant difference was observed only in OSDI scores among dry eye parameters, with Group 2 having significantly higher OSDI scores ($p=0.019$). According to the Oxford scale, only Group 1 had significantly higher scores than Group 3 ($p=0.021$). The measured endothelial cell density, coefficient of variation, and percentage of hexagonal cells values were not significantly different among the groups ($p>0.05$).

Conclusion: Repeated IVIs may contribute to ocular surface inflammation through multiple mechanisms, including exposure to povidone-iodine and preservatives present in topical eye drops. The cumulative exposure associated with frequent injections could exacerbate this inflammatory response, potentially leading to ocular surface damage. The burden of IVIs or the presence of nAMD does not appear to affect corneal endothelial function.

Keywords: Corneal endothelium, Dry eye, Intravitreal injection, Neovascular age-related macular degeneration

Age-related macular degeneration (AMD) is indeed a significant cause of vision impairment globally.[1] Neovascular AMD (nAMD), a late-stage manifestation, is distinguished by the presence of subretinal fluid, hemorrhage, and fibrosis secondary to choroidal neovascularization. The primary therapeutic target is vascular endothelial growth factor (VEGF), which plays a crucial role in angiogenesis and vascular permeability—key features of nAMD

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pathophysiology.[2] The advent of anti-VEGF (anti-VEGF) therapies has revolutionized the therapeutic landscape for patients diagnosed with nAMD. Over the past decade and a half, the application of intravitreal injection (IVI) of anti-VEGF agents has undergone a remarkable expansion, solidifying its position as the most frequently performed intraocular procedure globally.[2,3] While demonstrating exceptional efficacy in preserving visual acuity and tolerability, the inherent nature of macular disease progression necessitates repetitive, iterative anti-VEGF treatment regimens spanning months to years.[4]

IVIs can induce a range of short-term adverse effects, including subconjunctival hemorrhage, intraocular floaters, and elevated intraocular pressure (IOP).[5] However, the most dreaded adverse event is endophthalmitis.[5] To reduce this risk, meticulous protocols are employed, including the utilization of povidone-iodine for its potent periocular and ocular surface sterilization properties. In addition, post-injection antibiotic prophylaxis is implemented. Nevertheless, literature has documented that topical application of 5% povidone-iodine to the ocular surface may disrupt corneal and conjunctival epithelial integrity, leading to reports of visual impairment, burning, or stinging sensations.[6] The use of post-injection prophylactic antibiotics containing preservatives can also induce ocular surface irritation and corneal/conjunctival tissue damage.[7] Even seemingly innocuous practices, such as the administration of preservative-containing eye drops once daily for a week, can alter the ocular surface and contribute to dry eye symptomatology.[8]

Emerging evidence suggests that the corneal endothelium expresses VEGF receptors,[9] implicating VEGF signaling in its physiological functions. Notably, IVIs of anti-VEGF agents, commonly used for the treatment of retinal diseases, have been detected within the aqueous humor.[10,11] Previous studies have compared ocular surface and anterior segment parameters in nAMD patients receiving IVI in one eye versus the fellow eye.[12-14] In the present study, we aimed to evaluate ocular surface parameters and the impact of IVI on corneal endothelium in patients newly indicated for IVI compared to those with a history of multiple IVI procedures.

Materials and Methods

This study employed a cross-sectional design and was conducted in the Department of Ophthalmology between June 2022 and May 2023. The study protocol received ethical approval from the Clinical Research Ethics Committee (2024/5). All participants provided written informed consent, and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

Group 1 comprised 261 nAMD patients who had received at least three IVIs of anti-VEGF agents (aflibercept, ranibizumab, or bevacizumab) in both eyes for choroidal neovascularization, while Group 2 consisted of 115 patients who had recently been diagnosed with nAMD and had no prior history of IVI. Finally, Group 3 consisted of 92 healthy age- and sex-matched participants. Participants in Group 1 who received monthly IVIs were recalled for evaluation 28 days after the last injection, and the eye that had received more IVIs was included in the study. The right eyes of participants in Groups 2 and 3 were included in the study. Participants in Group 3 were recruited from patients who presented to the clinic for routine ophthalmological examinations or with presbyopic complaints. Each subject completed the Ocular Surface Disease Index (OSDI) questionnaire and then underwent a complete ophthalmic examination, including best-corrected visual acuity measurement (BCVA) (logMAR), IOP measurement using a pneumatic tonometer, slit lamp and specular microscopy examinations, evaluation of tear break-up time (TBUT), the Schirmer I test, and the Oxford Grading Scale. Finally, a dilated fundoscopic examination and fundus fluorescein angiography was performed to eliminate the potential effect of mydriatic medications on the ocular surface.

The severity of dry eye symptoms was assessed using a validated tool, the OSDI questionnaire. The OSDI utilizes a 0–100-point scale, where higher scores correspond to greater disease severity. Standardized Schirmer tear test strips were inserted for 5 min, or until fully saturated with tears. Tear production was measured in millimeters based on the markings on the strip. TBUT was measured by recording the time elapsed until the first dry spots appeared on the cornea following the instillation of topical 0.5% fluorescein. The fluorescein staining technique was identical to that employed in the TBUT assessment. Corneal punctate staining was evaluated using the Oxford Grading Scale, ranging from 0 to 5.[15] Individuals with a history of corneal diseases like corneal opacity, interstitial keratitis, or corneal dystrophies, those whose corneal endothelial count was <2000 cells/mm^2, prior ocular surgery other than cataract, dermatologic or systemic disease that could potentially affect the ocular surface, recent contact lens use, and use of regular topical drops, including artificial tears, were excluded from the study. The refractive error of the subjects was limited to ±6.00 spherical and ±3.00 cylindrical diopters.

Injection Technique

Following topical anesthesia with proparacaine (Alcaine 0.5%, Alcon AG, Switzerland), the eyelid and surrounding periocular region were disinfected with 10% povidone-iodine and draped with a sterile ophthalmic surgical drape. Subsequently, 5% povidone-iodine solution was instilled into the cornea, conjunctiva, and palpebral fornixes. This solution remained in place for 3 min before being thoroughly irrigated with a balanced sterile saline solution. The anti-VEGF agent was injected intravitreally using a 30-gauge needle. The injection site was located 3.5 mm from the limbus within the superotemporal quadrant. The eye was then maintained in a closed position for a period of 4 h. To minimize the risk of post-operative infection, topical moxifloxacin hydrochloride (Moxai 0.5%, Abdi Ibrahim, Türkiye) was administered 5 times daily for 5 days.

Specular Microscopy Measurements

Corneal endothelial cell analysis was carried out using specular microscopy (Konan, CellChek XL, Konan Medical, CA) by an experienced examiner. The specular microscopy examination was performed between 10 and 11 a.m. under constant temperature (24–27°C) and humidity (40–50%) conditions. The patient was asked to focus on the internal fixation point inside the device. The device captures an endothelial image of a standardized area of 0.1 mm^2. This study opted for the fully automated analysis mode with predefined cell size settings. In this mode, the software utilizes default size references categorized from "Small" to "XLarge" and automatically selects the "Small" category for analysis. To ensure data consistency, three images were captured for each sample and stored within the device's internal database. Three consecutive measurements were performed, and the mean value of these measurements was considered for the statistical analysis. Endothelial cell density (ECD) (cells/mm^2), coefficient of variation (CV) (%), percentage of hexagonal cells (HEX) (%), and central corneal thickness (CCT) (μm) were recorded and analyzed for each eye.

Statistical Analysis

Statistical analysis was performed using SPSS, version 26.0, for Windows (IBM Corporation, Armonk, NY). Descriptive statistics are presented as numbers and percentages for categorical variables and mean and standard deviation for numerical variables. The Kolmogorov–Smirnov test was used to determine the numerical data distribution. The differences in specular microscopy and dry eye measurements among the groups were assessed with analysis of variance (ANOVA) test. Post hoc tests were performed to analyze the significance of differences in pairs of values. Pearson correlation was applied to test the correlation between the variables. Statistical significance was set at $p<0.05$.

Results

The study included 242 females and 226 males, and the mean age was 74.8±8.4, 73.6±9.1, and 75.1±7.4 years in groups 1, 2, and 3, respectively. There were no significant differences among the groups in terms of gender and age distribution ($p>0.05$). Considering only the eyes that received more injections in Group 1, the mean number of IVIS was 9.12 (3–21). The mean preoperative BCVA values were not significantly different between groups 1 and 2 ($p=0.342$), while these values were significantly lower than those in group 3 ($p<0.001$ for two comparisons). The participants' clinical and demographic characteristics are presented in Table 1.

OSDI scores were highest in Group 1 and lowest in Group 3, with significant differences between all groups ($p<0.05$). When TBUT and Schirmer values were examined, there was no significant difference between non-injected nAMD patients (Group 2) and healthy individuals (Group 3) ($p=0.112$, post hoc test), while the injected group (Group

Table 1. Demographic and clinical characteristics of the participants

	Group 1 (n=261) Mean±SD	Group 2 (n=115) Mean±SD	Group 3 (n=92) Mean±SD	P*
Gender (M/F)	125/136	53/62	43/49	0.231
Age (years)	74.8±8.4	73.6±9.1	75.1±7.4	0.144
Axial length (mm)	23.06±0.72	23.18±0.69	23.11±0.97	0.342
Intraocular pressure (mmHg)	17.01±2.99	16.42±3.21	15.98±4.12	0.211
Spherical equivalent (diopter)	−0.53±0.98	−0.60±1.01	−0.49±1.12	0.059
BCVA (logMAR)	0.52±0.39	0.55±0.41	0.06±0.19	<0.001

SD: Standard deviation; BCVA: Best-corrected visual acuity; *The analysis of variance (ANOVA) test, Bold font indicates statistical significance.

1) had significantly lower values than the other groups ($p<0.05$, post hoc tests). In corneal staining scores (Oxford scale), there was only a significant difference between Group 1 and Group 3, and Group 1 had significantly higher values ($p=0.021$) (Table 2).

The measured ECD, CV, and HEX values were not statistically significantly different among the groups. CCT measurements were significantly thinner in Group 1 compared to Groups 2 and 3 ($p=0.044$ and $p=0.011$, respectively). In Group 1, the number of IVIs was positively correlated with OSDI scores ($r=0.432$, $p=0.002$), and negatively correlated with TBUT ($r=-0.626$, $p<0.001$) and Schirmer values ($r=-0.598$, $p<0.01$) (Table 2).

Discussion

Dry eye disease (DED) is a multifactorial disease affecting the tear film and ocular surface. It manifests as ocular discomfort and compromises visual function.[16] Dysfunction in any component of the lacrimal functional unit, encompassing the lacrimal gland, ocular surface, eyelids, and associated neural innervation, can contribute to DED.[16] This condition demonstrates a significant prevalence increase within the elderly population, affecting an estimated 5–30% of individuals exceeding 60 years of age,[16] Several age-related factors predispose older adults to DED. These include a decline in lacrimal gland function leading to decreased tear production, eyelid laxity impacting tear film distribution, and hormonal fluctuations associated with menopause in women.[17,18] In addition, the increased use of systemic and topical medications in elderly patients can exacerbate DED. Furthermore, chronic inflammatory conditions and elevated oxidative stress, both hallmarks of the aging process, contribute to the development and progression of DED.[17,18] The demographic shift toward an aging population with an increasing life expectancy underscores the growing public health concern surrounding DED. As the number of individuals exceeding 60 years of age continues to rise, a corresponding increase in the prevalence of DED is anticipated. While high-contrast visual acuity may remain unaffected or minimally impacted, individuals with DED often suffer from debilitating discomfort and functional vision limitations.[16] Notably, a study investigating the impact of severe DED on patients' quality of life yielded results comparable to those reported for patients with moderate-to-severe angina or undergoing dialysis.[19] Considering that aging is one of the most important risk factors for AMD and that these patients experience a wide range of visual impairments, dry eye-related additional visual complaints and a possible decrease in quality of life can make living conditions even more challenging. In this study, we also observed that the dry eye examination findings (increased OSDI scores and decreased TBUT and Schirmer 1 values) in monthly injected nAMD patients were more significant compared to those in non-injected nAMD patients and healthy individuals.

Anti-VEGF agents represent the current gold standard for nAMD treatment, necessitating repeated IVIs for most patients.[20] However, this therapeutic approach necessitates a prolonged course, frequently leading to complaints of dry eye symptoms among patients. The repetitive nature of the treatment, coupled with the required antiseptic precautions, exposes the ocular surface to increased inflammatory stress, potentially triggering the development of dry eye syndrome. Experimental and clinical evidence strongly supports the role of

Table 2. Ocular surface and specular microscopy parameters of the participants

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Group 3 (Mean±SD)	P*
OSDI score	29.4±16.5	19.9±14.4	13.8±11.6	<0.001
TBUT (s)	8.7±4.3	11.8±3.9	12.1±4.2	<0.001
Schirmer I (mm)	10.6±6.9	13.1±7.6	14.2±6.6	0.004
Oxford Grading Scale	0.61±0.59	0.54±0.31	0.50±0.44	0.021
ECD (cell/mm2)	2601.3±241.6	2643.8±299.1	2638.2±259.9	0.106
CV (%)	47.6±7.1	46.1±6.9	45.9±6.6	0.079
HEX (%)	41.8±6.6	43.7±7.1	42.9±6.3	0.324
CCT (µm)	511.6±39.9	523.1±44.2	519.4±43.3	0.002

SD: Standard deviation; OSDI: Ocular surface disease index; TBUT: Tear break-up time; ECD: Endothelial cell density; CV: Coefficient of variation; HEX: Percentage of hexagonal cells. CCT: Central corneal thickness. *The analysis of variance (ANOVA) test, Bold font indicates statistical significance.

immunological processes in AMD pathogenesis.[21,22] Considering the role of inflammation in AMD and DED pathophysiology, we also aimed to compare IVI-naive patients with healthy individuals. Notably, only OSDI scores were significantly higher in IVI-naive patients compared to healthy individuals. The subjective design of the OSDI questionnaire and the inclusion of questions on blurred and poor vision in it may have contributed to the higher scores observed in nAMD patients.

Following IVIs, the routine use of short-term topical antibiotics is employed by most ophthalmologists to reduce the risk of endophthalmitis.[23] However, the preservatives commonly found in topical ophthalmic preparations have been implicated in contributing to ocular surface inflammation, potentially leading to the development of DED.[24] In this context, single-use, preservative-free topical agents offer a valuable option for preventing iatrogenic inflammation and minimizing patient discomfort.[24] Dohlman et al. have reported acute epitheliopathy associated with topical anesthesia in addition to povidone iodine in patients undergoing IVI treatment.[25] Verrecchia et al. further presented that dry eye symptoms following IVIs are not limited to the acute phase and also persist in the long term.[26]

In our literature review, we observed that there is no complete consensus regarding the direct impact of VEGF on the ocular surface. While some studies suggest that VEGF has a positive effect on corneal healing and that anti-VEGF agents may mitigate this effect,[25,27] other studies propose that VEGF has pro-inflammatory effects that could be diminished with IVIs and even alleviate dry eye symptoms.[28,29] In addition, Roda et al. reported a significant increase in VEGF levels in the tears of patients with DED. In our study, patients undergoing IVI therapy exhibited significantly higher OSDI scores and significantly lower TBUT and Schirmer test values. In contrast to numerous studies, including the present study, Malmin et al. proposed that despite the limited systemic penetration of anti-VEGF agents in intravitreal usage, these therapies may reduce ocular surface inflammation and reduce lid margin inflammation and telangiectasias observed in patients with meibomian gland dysfunction.[29] Furthermore, they reported that regular application of povidone iodine may contribute to a decreased bacterial load, potentially decreasing dry eye symptoms, especially in infectious conditions like blepharitis.[29]

The RE-VIEW study stands as the most comprehensive investigation to date, employing the longest follow-up period, to assess the impact of repeated IVI of anti-VEGF agents on the corneal endothelium.[13] Notably, the RE-VIEW findings revealed no statistically significant alteration in ECD within a 1-year timeframe for eyes receiving IVI,[13] and the observed change remained consistent with the expected decline in corneal endothelial cells associated with the natural aging process.[30] Furthermore, no clinically significant difference was identified compared to the fellow eyes that did not receive treatment over the same period. In the studies conducted by Yoeruek et al. and Hosny et al., there were no significant differences in corneal endothelial parameters immediately after and at the 6-month follow-up period following IVI therapy. Notably, apart from IVI of anti-VEGFs, these agents have not exhibited any toxic effects, even when administered intracamerally or in corneal endothelial cell cultures.[31,32] Similarly, our study found no significant differences in ECD, CV, and HEX parameters among the three groups, the only CCT values were significantly thinner in patients receiving IVI therapy compared to the other groups. While previous studies have not demonstrated an association between neovascular or non-neovascular AMD and corneal thickness,[33,34] some reports suggest that corneal thickness may be reduced in dry eye patients, which aligns with our findings.[35,36]

Since patients in the injection group of this study received IVIs in both eyes, we were unable to directly compare the injected and healthy eye in same patient. In addition, our study included previously untreated nAMD patients and healthy individuals for comparison. Previous researches have demonstrated increased dry eye findings in the healthy eyes of individuals with unilateral quiescent stromal herpetic keratitis and unilaterally corneal nerve-sectioned mice.[37-39] These findings also provide valuable support for our comparison of patients who underwent IVI therapy and those who did not.

Our study has some limitations. First, due to the cross-sectional nature of the study, it does not include pre- and post-injection examination findings or long-term follow-up of the patients. Second, the subjectivity of the OSDI scoring system may have led to higher scores for patients with AMD-related vision loss. Third, more objective data, such as tear osmolarity and confocal microscopy evaluation, could not be used to support the data when evaluating patients' ocular surface parameters. Finally, the patient outcomes were evaluated without considering which anti-VEGF agents (aflibercept, ranibizumab, and bevacizumab) were administered to nAMD patients.

Conclusion

nAMD frequently necessitates repetitive IVI therapy, which may lead to an accumulation of toxic effects from povidone-iodine, topical anesthetics, and antibiotics. In this study, nAMD patients who underwent IVI therapy exhibited significantly higher OSDI scores and lower TBUT and Schirmer values compared to those who did not receive IVI therapy and healthy individuals. In addition, no significant differences in corneal endothelial function were observed among the groups. Ophthalmologists should recognize the susceptibility of nAMD patients to ocular surface inflammation and dry eye, arising from both their age and the gold standard treatment for this retinal disease, IVI of anti-VEGF agents.

Ethics Committee Approval: This study was approved by Niğde Ömer Halisdemir University Faculty of Medicine Ethics Committee (2024/5).

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