



Dry Eye and Meibomian Gland Dysfunction in Neovascular Age-Related Macular Degeneration Patients Treated with Intravitreal Injections

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Abstract

Objectives: To determine if patients treated with multiple intravitreal injections for neovascular age-related macular degeneration are more likely to suffer from dry eye and meibomian gland dysfunction.

Materials and Methods: Sixty eyes of 30 patients were enrolled. One eye of each patient was treated with multiple monthly intravitreal injections for neovascular AMD (Group 1) and the fellow healthy eye received no treatment (Group 2). The presence of dry eye was evaluated using tear film break-up time, Schirmer 1 test, the Oxford scale, and Ocular Surface Disease Index (OSDI). The loss rate of meibomian glands was evaluated by meibography and was graded and scored (meiboscore) from grade 0 (no loss of glands) to grade 3 (loss of >2/3 of total meibomian glands) for each eyelid.

Results: Group 1 had lower mean Schirmer 1 and tear film break up-time measurements and higher mean OSDI score than Group 2, but the differences were not statistically significant ($p=0.257$, $p=0.113$, and $p=0.212$, respectively). Mean Oxford scale scores and meiboscore of the upper eyelids showed no statistically significant difference between the groups ($p=0.594$, $p=0.663$, respectively). The meiboscore of the lower eyelids was significantly higher in Group 1 ($p=0.048$).

Conclusion: Multiple factors such as povidone-iodine and the preservatives in topical eye drops may cause inflammation leading to ocular surface damage in patients treated with multiple intravitreal injections. As the treatment requires repeated injections, exposure to these factors might worsen the ocular surface inflammation. The possibility of dry eye and meibomian gland dysfunction should be considered in these patients.

Keywords: Intravitreal injection, neovascular age-related macular degeneration, dry eye, meibomian gland dysfunction, meibography

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Received: 14.10.2020 **Accepted:** 26.05.2021

Cite this article as: Kıyat P, Palamar M, Nalçacı S, Akkın C. Dry Eye and Meibomian Gland Dysfunction in Neovascular Age-Related Macular Degeneration Patients Treated with Intravitreal Injections. Turk J Ophthalmol 2022;52:157-161

Introduction

Age-related macular degeneration (AMD) is an important cause of blindness in older people in developed countries,¹ and the neovascular type requires treatment with anti-vascular endothelial growth factor (anti-VEGF) inhibitors.² In our daily practice, we noticed that AMD patients treated with intravitreal injections often complain about dry eye symptoms and seem more prone to meibomian gland dysfunction and dry eye in ophthalmic examinations. In addition, in previous studies it has been emphasized that patients treated with intravitreal injections reported grittiness and ocular pain very frequently.^{3,4}

Although different dosing regimens such as “as needed” (*pro re nata* [PRN]) or “treat and extend” are preferred to decrease injection frequency, treatment is repetitive and carries risks such as endophthalmitis.⁵ Ophthalmic povidone-iodine is routinely used to prevent endophthalmitis because of its wide antimicrobial activity and cost-effectiveness.⁶ Short-term topical antibiotic therapy is another option used by many ophthalmologists to prevent endophthalmitis, although some trials found ocular surface bacteria to be resistant to topical antibiotics.⁷ However, repetitive usage of these agents and the preservatives they contain might have an impact on the ocular surface and meibomian glands and contribute to damage in the long term. However, to our knowledge, no study to date has evaluated the relation between intravitreal injections and meibomian gland function with meibography.

Dry eye is a multifactorial ocular surface disease which reduces patients' quality of life.⁸ Meibomian gland dysfunction is one of the most important causes of dry eye syndrome.⁹ Meibomian glands can be imaged using many different tools performing meibography, and gland loss can be evaluated with the scoring systems defined in previous studies.¹⁰ In the 2017 TFOS Dry Eye Workshop, dry eye was identified as a disease in which inflammation plays a significant role.¹¹ Ocular surface inflammation is considered to be one of the main causative factors in aqueous deficiency and evaporative type dry eye disease, and the latter is correlated to meibomian gland dysfunction.^{11,12} Exaggerated and abnormal immune stimulation or disrupted immunoregulatory mechanisms resulting in dysregulation of the ocular surface immune system may cause dry eye disease.¹³

Previous studies mentioned the relation between inflammation-related diseases and meibomian gland dysfunction.^{14,15} We hypothesize that the intravitreal injection treatment procedure in AMD might lead to dry eye and have an impact on the meibomian glands.

The purpose of this study was to determine if patients treated with multiple intravitreal injections for neovascular AMD (nAMD) are more likely to suffer from dry eye and meibomian gland dysfunction in comparison to normal untreated eyes.

Materials and Methods

In the present study, 60 eyes of 30 patients were evaluated. Patients diagnosed with nAMD who had a minimum of 6 doses of monthly intravitreal ranibizumab and/or aflibercept

injections to only one eye were included. Patients who were treated in both eyes, received fewer than 6 intravitreal injections, received intravitreal injections for other retinal diseases such as diabetes, or had a history of ophthalmic surgery, preexisting dry eye disease, or any autoimmune disease that may be associated with dry eye were excluded. The eyes with nAMD that had at least 6 monthly intravitreal injections were evaluated as group 1 and the healthy, untreated fellow eyes of the same patients were evaluated as group 2. To prevent endophthalmitis, povidone-iodine (10%) was applied for 3 minutes before the injection and topical antibiotic (netilmicin, 4 times daily) was provided for a week after the injection.

All subjects included in the study underwent a detailed ophthalmological examination 4 weeks after the last injection. Dry eye tests were also performed on both treated and healthy eyes, including tear film break-up time (TBUT), Schirmer 1 test, corneal and conjunctival fluorescein staining and Oxford scoring, and Ocular Surface Disease Index (OSDI) assessment.

Evaluation of the upper and lower eyelid meibomian glands were performed using the infrared filter of a slit-lamp biomicroscope (Topcon, SL-D701, IJssel, Netherlands) and the loss rate of meibomian glands was graded and scored (meiboscore) for each eye. Gland loss was classified as grade 0 if there was no loss of the meibomian glands, grade 1 if the loss rate was less than 1/3 of the total meibomian glands, grade 2 if the loss rate was between 1/3 and 2/3 of the total meibomian glands, and grade 3 if the loss rate was more than 2/3 of the total meibomian glands.¹⁶ The meibomian gland dropout ratio was evaluated blindly by the same researcher (M.P). Meiboscores for the upper, lower, and total (upper+lower) eyelids were determined for each eye.

Statistical Analysis

Each subject provided written informed consent. The institutional review board of Ege University Hospital approved the study, which adhered to the tenets of the Declaration of Helsinki. For statistical analyses, the Statistical Package for the Social Sciences version 11.5.0 was used. A biostatistician was consulted for the data analysis.

Results

The mean age of the patients was 73.8±9.07 years (range, 61-86) (Table 1). The mean Schirmer 1 values in groups 1 and 2 were 19.2±4.8 mm (range, 10-30) and 20.3±4.4 mm (range, 12-30), respectively (p=0.257). The groups' respective mean TBUT values were 9.6±3.8 s (range, 3-18) and 11.3±4.1 s (range, 3-19) (p=0.113), mean Oxford scale (superficial punctate staining of the cornea and conjunctiva) scores were 0.6±0.7 (range, 0-2) and 0.6±0.7 (range, 0-2) (p=0.594), and mean OSDI values were 28.9±20.7 (range, 2.1-71.5) and 22.2±18.5 (range, 2.1-71.5) (p=0.212).

In Group 1, the mean upper meiboscore was 1.4±0.9 (range, 0-3), lower meiboscore was 0.9±0.8 (range, 0-3), and total meiboscore was 1.1±0.8 (range, 0-3). In Group 2, the mean upper meiboscore was 1.3±0.9 (range, 0-3), lower meiboscore

was 0.4 ± 0.7 (range, 0-2), and total meiboscore was 0.9 ± 0.7 (range, 0-2.5). The upper eyelid and total meiboscores were higher in Group 1 but the differences were not statistically significant ($p=0.663$, $p=0.211$, respectively). The meiboscore for the lower eyelids was significantly higher in Group 1 ($p=0.048$).

Discussion

Dry eye is an ocular surface disease with multifactorial pathogenesis including an inflammatory basis. It causes hyperosmolarity and elevated inflammatory mediators in the tear film which lead to ocular surface damage such as epithelial cell apoptosis and goblet cell death, resulting in more inflammation.^{17,18}

Neovascular AMD is an important cause of blindness among older people in developed countries.¹⁹ Anti-VEGF agents such as ranibizumab or aflibercept are the gold-standard therapy for nAMD and almost all patients require repeated intravitreal injections.²⁰ Treatment with intravitreal anti-VEGF injections is a prolonged repetitive procedure, after which many patients complain of dry eye-related symptoms. As the treatment and the antiseptic precautions have to be repeated, the ocular surface faces more inflammation, which can trigger dry eye syndrome. In this study, Schirmer 1 measurements and TBUT measurements were found to be lower and OSDI scores were found to be higher in eyes treated with at least six intravitreal injections compared to healthy untreated eyes, but the differences were not statistically significant. However, treated eyes had a significantly higher mean lower eyelid meiboscore.

The most serious but rare complication of anti-VEGF treatment is endophthalmitis. To prevent endophthalmitis, povidone-iodine is applied before the injection and topical antibiotics are provided after the injection. Povidone-iodine is an antiseptic agent which is preferred for its effectiveness and wide spectrum.²¹ However, repeated exposure to povidone-iodine can cause ocular inflammation. Jiang et al.²² showed that higher concentration (higher than 5%) and longer treatment (more than 2 minutes) lead to corneal epithelial and endothelial cell damage. Another study by Laude et al.²³ suggested that repeated exposure to povidone-iodine may cause discomfort in patients receiving intravitreal anti-VEGF agents.

After the injections, most practitioners prefer to use short-term topical antibiotics to prevent endophthalmitis.²⁴ The preservatives in topical preparations can contribute to ocular surface inflammation, which might also lead to dry eye disease.²⁵ Single-use preservative free topical agents can be useful to prevent toxic inflammation and reduce patient discomfort.^{26,27} In addition, oxybuprocaine was suggested to be responsible for epithelial corneal damage, and this damage was found to be correlated with the product's concentration.²⁸

A recently published article claimed that intravitreal injections induced ocular surface damage through the use of povidone-iodine and topical anesthetics.²⁹ In the same article it was also reported that TBUT was lower in the injected eye when compared to the healthy fellow eye of the same patients. The authors also emphasized that this treatment procedure could cause iatrogenic and chronic dry eye, not only temporary damage.²⁹

Another striking point is the anti-VEGF effect itself. A study by Pan et al.³⁰ showed that VEGF had a positive impact on corneal healing, suggesting that intravitreal anti-VEGF injections might have a role in delayed healing of corneal damage related to the procedure.

Ocular inflammation associated with intravitreal anti-VEGF injections is a well-documented phenomenon that can be categorized into two clinical manifestations.³¹ The first presentation is "acute-onset sterile inflammation," the clinical features of which can vary widely from subclinical anterior chamber inflammation to severe inflammation that can be misdiagnosed as endophthalmitis. Subclinical anterior chamber inflammation is a fairly common sign after anti-VEGF injections, seen at rates as high as 20% of patients.³¹ The second manifestation is a recently described one, 'delayed-onset inflammatory vasculitis' associated with brolocizumab.³² As a result, inflammation can occur after intravitreal anti-VEGF injections and the clinical manifestation can range broadly. On the other hand, a study by Karti et al.³³ suggested that intravitreal anti-VEGF injections can be beneficial in treating choroidal neovascularization secondary to inflammatory diseases such as noninfectious uveitis in terms of both visual and anatomical improvement. Anti-VEGF agents exert their beneficial effect in these cases by inhibiting VEGF locally and reducing choroidal

Table 1. The dry eye test results and meiboscores of eyes treated with intravitreal injections (group 1) and healthy fellow eyes (group 2) of the same patients.

	Group 1, mean \pm SD (range)	Group 2, mean \pm SD (range)	p value
Schirmer-1 (mm)	19.2 \pm 4.8 (10-30)	20.3 \pm 4.4 (12-30)	0.257
TBUT (s)	9.6 \pm 3.8 (3-18)	11.3 \pm 4.1 (3-19)	0.113
Oxford scale	0.6 \pm 0.7 (0-2)	0.6 \pm 0.7 (0-2)	0.594
OSDI score	28.9 \pm 20.7 (2.1-71.5)	22.2 \pm 18.5 (2.1-71.5)	0.212
Upper meiboscore	1.4 \pm 0.9 (0-3)	1.3 \pm 0.9 (0-3)	0.663
Lower meiboscore	0.9 \pm 0.8 (0-3)	0.4 \pm 0.7 (0-2)	0.048
Total meiboscore	1.1 \pm 0.8 (0-3)	0.9 \pm 0.7 (0-2.5)	0.211

SD: Standard deviation, TBUT: Tear film break-up time, OSDI: Ocular Surface Disease Index

vascular permeability. However, as emphasized in the study, it is crucial to treat inflammation, mainly with steroids or immunosuppressive agents.

Povidone-iodine has antibacterial properties that can be protective against ocular surface damage associated with eyelid margin diseases. However, in our study patients with eyelid margin diseases did not receive any intravitreal injections in order to prevent endophthalmitis.

Dry eye disease is common in older adults. Age-related diseases or comorbid conditions such as diabetes also cause nerve damage and may increase the likelihood of dry eye. In most cases it is difficult to identify whether dry eye is caused by treatment or age-related changes. However, in the present study, the control group comprised the fellow eyes of the study group, which means that there is no variation in the age and systemic or ocular comorbid diseases between the treated and control groups. Therefore, we can effectively evaluate the effect of the treatment procedure.

Study Limitations

Evaluating meibomian gland dysfunction with meibography has become important in demonstrating the pathogenesis of dry eye disease. Previous studies showed that meibomian gland dysfunction is associated with inflammatory systemic diseases such as rosacea³⁴ or vitiligo³⁵ and ocular conditions such as pseudophakic bullous keratopathy³⁶ or contact lens usage.³⁷ However, to our knowledge, there has been no study to date evaluating meibomian gland function in patients treated with intravitreal injections. In the present study, meiboscores of the lower lids were higher in treated eyes than untreated eyes. This result might be the consequence of greater exposure of the inferior eyelid and meibomian glands to topical antibiotics and povidone-iodine.

Conclusion

In summary, AMD requires treatment with intravitreal injections. Although intravitreal anti-VEGF therapy is the gold standard, these patients may suffer from dry eye and/or meibomian gland dysfunction. In our study, we found statistically significant differences in meibomian gland dropout ratio, although treated eyes showed no significant differences in the dry eye tests. Still, we advise ophthalmologists to be vigilant for dry eye development and meibomian gland dysfunction in these patients. Due to the chronic nature of the treatment protocols, prolonged and repeated exposure to povidone-iodine, topical antibiotics, topical anesthetics, and preservatives in eye drops might predispose to ocular surface inflammation. OSDI scoring before multiple injections can help diagnose dry eye earlier. More studies with larger patient numbers are needed to understand the effect of intravitreal injection treatment procedures on the ocular surface.

Ethics

Ethics Committee Approval: The institutional review board 68 of Ege University Hospital no: 19-6.1T/45

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: P.K., M.P., S.N., C.A., Design: P.K., M.P., S.N., C.A., Data Collection or Processing: P.K., M.P., S.N., C.A., Analysis or Interpretation: P.K., M.P., S.N., C.A., Literature Search: P.K., M.P., S.N., C.A., Writing: P.K., M.P., S.N., C.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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