DOI: 10.4274/tjo.galenos.2021.66168
Turk J Ophthalmol

Original Article

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.

Methods: Sixty eyes of 30 patients were enrolled. Patients had one eye that was treated with multipl monthly intavitreal injections for neovascular age-related macular degeneration and one eye which was not treated. Group 1 included the treated eyes and Group 2 the untreated healthy ones. The existence of dry eye was tested with tear film break-up time, Schirmer-1 test, Oxford scale and Ocular Surface Disease Index (OSDI) score assessments. The loss rate of Meibomian glands was evaluated by meibography and was graded and analysed for each eyelid from grade 0 (no loss of the glands) to grade 3 (gland loss rate is higer than >2/3 of the total Meibomian glands).

Results: Mean Schirmer 1 and tear film break up-time measurements appeared lower (p=0.257, p=0.113, respectively), mean OSDI score appeared higher in Group 1 (p=0.212) but the differences were not statictically significant. Mean Oxford scale scores and meiboscore of upper eyelids did not show any statistically significant difference in Group 1 (p=0.594,p=0.663, respectively). The meiboscore for lower eyelids was higher in Group 1 and the difference was statistically significant (p=0.048).

Conclusion: Multipl factors such as povidone–iodine, preservatives in topical eye drops may cause inflammation leading to ocular surface damage in patients treated with multipl 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 dysfunction formation in these patients should be considered.

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

Introduction

Age-related macular degeneration (AMD) is an important reason for blindness in elder people in developed countries[1] and neovascular type requires treatment with anti-vascular endothelial growth factor (anti-VEGF) inhibitors.[2] In daily practice, in our opinion, patients with AMD treated with intravitreal injections often complain about dry eye symptoms and in ophthalmic examinations it seems like these patients are more prone to meibomian gland dysfunction and dry eye. Also in previous studies it has been emphasized that patients treated with intavitreal injections reported grittiness and ocular pain very frequently.[3,4]

Although different dosing regimens like 'as needed' (PRN) or 'treat and extend' are preferred[5] to decrease injection frequency, the treatment is repetitive and consists risks such as endophtalmitis. To prevent endophtalmitis, ophtalmic povidone-iodine is routinely used because of its wide antimicrobial activity and cost-effectiveness[6]. The short term usage of topical antibiotics is another option, for a significant percentage of ophthalmologists to prevent endophtalmitis, although some trials found ocular surface bacteria to be resistant to topical antibiotics[7]. However, repetitive usage of these agents and the preservatives in them might have an impact on ocular surface and meibomian glands and might be the contributing factors that lead damage in long term. However, to our knowledge, no study to date has evaluated the relation between intravitreal injections and meibomian gland functions 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 reason for dry eye syndrome[9]. Meibomian glands can be imaged by using many different tools performing meibography and the gland loss can be evaluated by the scoring systems defined in previous studies[10]. In TFOS Dry Eye Workshop, which took place at 2017, dry eye was identified as a disease related with significant role of inflammation[11]. Ocular surface inflammation is considered to be one of the main reasons 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 distrupted immunoregulatory mechanisms resulting in disregulation of immune system on ocular surface may cause dry eye disease.[13]

Previous studies mentioned about the relation between inflammatory related diseases and meibomian gland dysfunction.[14,15] We hypothesize that the treatment procedure in AMD with intravitreal injections might lead to dry eye and might has an impact on meibomian glands.

The purpose of this study is to determine if patients treated with multiple intravitreal injections for n-AMD 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 n-AMD and 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, who had less than 6 doses of intravitreal injections or had intravitreal injections for other retinal diseases such as diabetes, medical history with any ophthalmic surgeries, had pre-existing dry eye disease or the history of autoimmune disease that may be associated with dry eye were excluded. The eyes that were n-AMD diagnosed and had at least 6 monthly intravitreal injections were considered as Group 1 and the other healthy, untreated eyes of the same patients were considered as Group 2. In the intravitreal injection procedure, to prevent endophthalmitis, povidone-iodine (10%) was applied for three minutes before the injection and topical antibiotics (netilmicin) (4x1) were provided after the injection for a week.

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

Evaluation of upper and lower eyelid meibomian glands were performed using infrared filter of slit-lamp biomicroscope (Topcon, SL-D701, IJssel, The Netherlands) and the loss rate of meibomian glands' was scored for each eye. No loss of the meibomian glands was defined as 'grade 0'. If the loss rate in glands was less than 1/3 of the total meibomian glands than it was defined as 'grade 1'. If the loss rate in glands was in between 1/3 and 2/3 of the total meibomian glands than it was defined as 'grade 2'. Finally if the loss rate in glands was more than 2/3 of the total meibomian glands than it was defined as 'grade 3'[16]. Meibomian glands' drop-out ratio was evaluated blindly by the same researcher (MP). The meiboscores for the upper, lower and total (upper+lower) eyelids were summed up for each eye.

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

Results

The average age of the patients was 73.8 ± 9.07 (range, 61-86) (Table-1). Group 1's mean Schirmer 1 value was 19.2±4.8 (range, 10-30) and Group 2's was 20.3±4.4 (range, 12-30) mm, (p=0.257). Group 1's mean T-BUT value was 9.6±3.8 (range, 3-18) and Group 2's was 11.3±4.1 (range, 3-19) seconds, (p=0.113). Group 1's mean Oxford scale (superficial punctate staining of the cornea and conjunctiva) was 0.6 ±0.7 (range, 0-2) and Group 2's was 0.6±0.7 (range, 0-2), (p=0.594). Group 1's mean OSDI score was 28.9±20.7 (range, 2.1-71.5) and Group 2's was 22.2±18.5 (range, 2.1-71.5), (p=0.212).

Group 1's mean upper mebioscore was 1.4±0.9 (range, 0-3), lower mebioscore was 0.9±0.8 (range, 0-3) and total meiboscore was 1.1±0.8 (range, 0-3). Group 2's 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 meiboscores for upper eyelids and total eyelids were higher in Group 1 but the difference was not statistically significant (p=0.663, p=0.211 respectively). The meiboscore for lower eyelids was higher in Group 1 and the difference was statistically significant (p=0.048).

Discussion

Dry eye is an ocular surface disease with multifactorial pathogenesis including inflammatory basis. It causes hyperosmolarity[17] and elevated inflammatory mediators in the tear film which lead to ocular surface damage such as apoptosis of the epithelial cells and death of goblet cells, results with more inflammation[18]. Neovascular AMD is an important reason for blindness amongst the elder people in developed countries[19]. Anti-VEGF agents such as ranibizumab or aflibercept are the gold standard therapy for n-AMD and almost all patients require repeated intravitreal injections[20]. The 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 might trigger dry eye syndrome. Herein, the Schirmer 1 measurements and T-BUT measurements were found to be lower, OSDI scores were found to be higher in Group 1. However, the differences were not statistically significant. The mean lower eyelid meiboscore was high in Group 1 and the difference was statistically significant.

The most serious but rare side effect of the 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 be the cause of ocular inflammation. Jiang and colleagues[22] in a study showed that higher concentration (higher than %5) and longer treatment (more than 2 minutes) lead to corneal epithelium and endothelium cell damage. Another study by Laude and colleagues[23] suggested that repeated exposure to povidone-iodine can be the cause of 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 the topical drug can be the reason for ocular surface inflammation which also might lead to dry eye disease[25]. Single use preservative free topical agents can be useful to prevent toxic inflammation and reduce the patients' discomfort[26,27]. In addition, oxybuprocaine was suggested to be responsible for epithelial corneal damage, and the damage was found to be correlated with the product's concentration.[28]

The intravitreal injections were considered to be responsible to induce ocular surface damage via povidone iodine usage and topical anesthetics in a recently published article [29] Also in the same article it was reported that T-BUT in the injected eye was found to be lower when compared to the other healthy eye of the same patients. The authors also emphasized that this treatment procedure could cause iatrogenic and chronic dry eye, not only the temporarily damage.[29]

Another striking point is the anti-VEGF effect itself. In a study by Pan et al.[30] it was shown that VEGF had a positive impact on corneal healing so intravitreal anti-VEGF injections might have a role in delayed healing of corneal damage related with the procedure.

Intravitreal anti-VEGF injections associated with ocular inflammation is well documented phenomenon which can be categorized into two clinical manifestations.[31] First presentation is 'acute onset sterile inflammation' which the clinical features can vary widely from subclinical anterior chamber infammation to serious inflammation that can be misdiagnosed as endophthalmitis. Subclinical anterior chamber infammation is a quite common sign after anti-VEGF injections, the rates are high as 20% of the patients.[31] Second manifestation is a recently described one, 'delayed onset infammatory vasculitis' related with brolucizumab.[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] has been suggested that intravitreal anti-VEGF injections can be beneficial in treating choroidal neovascularization secondary to inflammatory diseases such as non-infectious type of uveitis in terms of both visual and anatomical improvement. Anti-VEGF agents show their beneficial effect in these cases by inhibiting VEGF locally and reducing the choroidal vascular permeability

Table 1. The dry eye tests and meiboscores of the groups.

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

however like it has been emphasized in the study, it is crucial to treat inflammation with steroids or immunosuppressive agents mainly.

Povidone-iodine has an antibacterial properties which can be protective against eyelid margin diseases related ocular surface damage however in our study no patients with eyelid margin diseases were injected intravitreal injections to reduce endophtalmitis risk.

Dry eye disease is common amongst the elderly. Age-related diseases or comorbid diseases such as diabetes, also cause nerve damage and may increase the likelihood of dry eye. Most of the times it is difficult to identify whether the cause of dry eye is the treatment or age-related changes. However, in the present study, the control group is 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 patient and the control groups. For this reason, we can effectively evaluate the effect of the treatment procedure.

Meibomian gland dysfunction evaluation with meibography gained importance to demonstrate the pathogenesis of the dry eye disease. Previous studies showed that inflammatuary systemic diseases such as rosacea[34] or vitiligo[35] and ocular conditions such as pseudophakic bullous keratopathy[36] or contact lens usage[37] are related to meibomian gland dysfunction. However to our knowledge, there was no study evaluating the meibomian gland function in patients treated with intravitreal injections to date. In the present study, meiboscores of lower lids in Group 1 is higher than Group 2. This result might be the consequence of higher 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 injection treatment is gold standard, these patients can suffer from dry eye and/or meibomian gland dysfunction. In our study, we found statistically significant differences in meibomian gland dropout ratio however there were no statistically significant differences among the dry eye tests in the treated eyes. Still we suggest ophthalmologists to be careful for dry eye development and meibomian gland dysfunction in these patients. Prolonged and repeated exposure to povidone–iodine, topical antibiotics, topical anesthetics and preservatives in eye drops, due to the treatment protocoles' chronic nature, might create a tendency to ocular surface inflammation. OSDI scoring before prior to multiple injections can help to diagnose dry eye earlier. More studies with higher number of patients are needed to understand the effect of the intravitreal injection treatment procedures on the ocular surface.

*The study was approved by Institutional Ethics Committee of xxx University and followed the tenets of Helsinki Declaration.

References

1. Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, Nemesure B, Mitchell P, Kempen J . Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004;122(4):564–572.
2. Klaver CC, Wolfs RC, Vingerling JR, Hofman A, de Jong PT. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam study. *Arch Ophthalmol* 1998;116(5):653–658.
3. Saedon H, Nosek J, Phillips J, Narendran N, Yang YC. Ocular surface effects of repeated application of povidone iodine in patients receiving frequent intravitreal injections. Cutan Ocul Toxicol 2017;36(4):343-346.
4. Oakley C, Allen P, Hooshmand J, Vote BJT. Pain and antisepsis after ocular administration of povidone-iodine versus chlorhexidine. Retina 2018; 38: 2064–2066.
5. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537–2548.
6. Grzybowski A, Kanclerz P, Myers WG. The use of povidone-iodine in ophthalmology. *Curr Opin Ophthalmol* 2018;29(1):19–32.
7. Hsu J, Gerstenblith AT, Garg SJ, Vander JF Conjunctival flora antibiotic resistance patterns after serial intravitreal injections without postinjection topical antibiotics. *Am J Ophthalmol.* 2014;157(3):514-8.
8. Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The immunological basis of dry eye disease and current topical treatment options. *J Ocul Pharmacol Ther* 2020; 36(3):137-146.
9. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, Na KS, Schaumberg D, Uchino M, Vehof J, Viso E, Vitale S, Jones L. TFOS DEWS II epidemiology report. *Ocul Surf* 2017;15(3):334-65.
10. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, Foulks GN. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. *Invest Ophthalmol Vis Sci* 2011;52(4):1930-7.
11. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15(3):276-83.
12. Knop E, Knop N, Millar T, Obata H, Sullivan D. The international workshop on Meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the Meibomian gland. *Invest Ophthalmol Vis Sci* 2011; 52(4):1938–1978.
13. Gagliano C, Visalli E, Toro MD, Amato R, Panta G, Scollo D, Scandura G, Ficili S, Amato G, Benenati A, Foti R, Malaguarnera G, Gagliano G, Falsaperla R, Avitabile T, Foti R. Dry eye in systemic sclerosis patients: Novel methods to monitor disease activity. *Diagnostics (Basel)* 2020;13 10(6):404.
14. Kiyat P, Palamar M, Gerceker Turk B, Yagci A. Dry eye and quantitative and qualitative changes of Meibomian glands in patients with pemphigus. *Cornea* 2020; 39(9):1108-1111.
15. Adiguzel S, Palamar M, Yargucu F, Oksel F, Yagci A. Evaluation of ocular surface and Meibomian glands in patients with scleroderma. Cornea 2020 Oct 19.
16. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. *Ophthalmology* 2008;115(5):911-5.
17. Calonge M, Enriquez-de-Salamanca A, Diebold Y, González-García MJ, Reinoso R, Herreras JM, Corell A. Dry eye disease as an inflammatory disorder. *Ocul Immunol Inflamm* 2010;18(4):244–253
18. Yeh S, Song XJ, Farley W, Li DQ, Stern ME, Pflugfelder SC. Apoptosis of ocular surface cells in experimentally induced dry eye. *Invest Ophthalmol Vis Sci* 2003;44(1):124–129.
19. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA* 2003;290(15):2057–2060.

20. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 2006;26(8):859–870.
21. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. *Ophthalmology* 1991;98(12):1769–1775.
22. Jiang J, Wu M, Shen T. The toxic effect of different concentrations of povidone iodine on the rabbit's cornea. *Cutan Ocul Toxicol* 2009;28(3):119–124.
23. Laude A, Lim JW, Srinagesh V, Tong L. The effect of intravitreal injections on dry eye, and proposed management strategies. *Clin Ophthalmol.* 2017;11:1491-1497.
24. Garg P, Roy A, Sharma S. Endophthalmitis after cataract surgery: epidemiology, risk factors, and evidence on protection. *Curr Opin Ophthalmol* 2017;28(1):67–72.
25. Mantelli F, Tranchina L, Lambiase A, Bonini S. Ocular surface damage by ophthalmic compounds. *Curr Opin Allergy Clin Immunol* 2011;11(5):464–470.
26. Mencucci R, Paladini I, Pellegrini-Giampietro DE, Menchini U, Scartabelli T. In vitro comparison of the cytotoxic effects of clinically available ophthalmic solutions of fluoroquinolones on human keratocytes. *Can J Ophthalmol* 2011;46(6):513–520.
27. Li XM, Zhao X, Hu LZ, Wang W. Clinical observation of dry eye in patients before and after cataract surgery. *Chin J Ophthalmol* 2007;43(1):10–13.
28. Brewitt H, Bonatz E,Honegger H. Morphological changes of the corneal epithelium after application of topical anaesthetic ointments. Ophthalmologica. 1980; 180:198-206.
29. Verrecchia S, Chiambaretta F, Kodjikian L, Nakouri Y, El Chehab H, Mathis T, Badri Y, Chudzinski R, Levron A, Chaperon M, Agard E, Pradat P, Dot C. A prospective multicentre study of intravitreal injections and ocular surface in 219 patients: IVIS study. *Acta Ophthalmol* 2021; Mar 18.
30. Pan Z, Fukuoka S, Karagianni N, Guaiquil VH, Rosenblatt MI. Vascular endothelial growth factor promotes anatomical and functional recovery of injured peripheral nerves in the avascular cornea. FASEB J 2013; 27: 2756–2767.
31. Anderson WJ, da Cruz NFS, Lima LH, Emerson GG, Rodrigues EB, Melo GB. Mechanisms of sterile inflammation after intravitreal injection of antiangiogenic drugs: a narrative review. Int J Retina Vitreous 2021; 7(1):37.
32. Cox JT, Eliott D, Sobrin L. Inflammatory complications of intravitreal anti-VEGF injections. J Clin Med 2021;10(5):981.
33. Karti O, Ipek SC, Ates Y, Saatci AO. Inflammatory choroidal neovascular membranes in patients with noninfectious uveitis: The place of intravitreal anti-VEGF therapy. Med Hypothesis Discov Innov Ophthalmol 2020; 9(2):118-126.
34. Palamar M, Degirmenci C, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in patients with rosacea. *Cornea* 2015;34(5):497-9.
35. Palamar M, Kiyat P, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in vitiligo. *Eye (Lond)* 2017;31(7):1074-1077.
36. Palamar M, Kiyat P, Yagci A. Dry eye and meibomian gland dysfunction in pseudophakic bullous keratopathy. *Int Ophthalmol* 2019;39(2):393-396.
37. Arita R, Fukuoka S, Morishige N. Meibomian gland dysfunction and contact lens discomfort. *Eye Contact Lens* 2017;43(1):17-22.