Research Article

Efficacy of Bevacizumab to Reduce Lid Margin Vascularity and Alteration in Tear Film Status

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Abstract

Objective: The purpose of this study is to observe the efficacy of a single injection of Bevacizumab into meibomian gland in decreasing eyelid margin vascularization and its effect on the level of the tear film.
Study Design: Quasi Experimental Study

Methods: Present study was carried out at Khalid Eye clinic, Karachi. It was done from April 2019 to July 2019 and incorporated eleven patients of either gender of an age range of 20 - 35 years. An inclusion criterion was blepharitis refractory to other treatment whereas patients less than 20 and greater than 35 years of age were excluded from this study. Patients were informed regarding the dynamics of this study and verbal consent was taken. The level of the tear film level was evaluated using Schirmer's test 2 (without anesthesia) followed by Bevacizumab injection into the eyelid from the conjunctival side. The chief conclusion was a reduction in eyelid margin vascularization from grade 3 to grade 1 and improvement in the level of the tear film post 30 days.

Results: This research incorporated eleven patients refractory to previous treatment for blepharitis and showed a noticeable reduction in the lid margin vascularity along with enhancement in the level of tear film one month post injecting Bevacizumab.

Conclusion: Bevacizumab is an effective treatment in terms of reduction of vascularity of the lid margin and improvement in the level of tear film among patients afflicted with blepharitis refractory to other treatments.

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Introduction:

A persistent lid margin inflammation, Blepharitis, may engage the corneal as well as conjunctival tissue. It is quite common and multiple factors are responsible for ocular discomfort, disturbed vision, and unsteadiness of the tear film along with consequent injury to the ocular surface.[1] Dysfunction of the meibomian gland (MGD) is one of the causes of blepharitis and involves the meibomian gland along with neighboring tissues of the eyelid leading to scales, eyelid notching, eyelid congestion and vascularity, lid margin hyperkeratosis, impediment of the ducts and disuse wasting of meibomian acini.[2] Vascularization and hyperemia of the eyelid margin usually present owing to an interaction with a variety of irritants ensuing a merger of numerous mechanisms, together with factors related to microbes, inflammation and lack of lipid.[3]

Traditional treatment for blepharitis comprises of maintaining hygiene, topical lubricants, and oral antibiotics as well as corticosteroids. Regardless of tradetional treatment blepharitis may advance to vascularization and scarring of the corneal surface.[4] Vascular Endothelial Growth Factor (VEGF) is the chief parameter for new vessel formation in inflamemation, healing of the wound, development of tumor tissue.[5] Studies have been done which report that

VEGF is a pro inflammatory factor to rouse the deliverance of inflammatory factors TNFα, IL6 and IL8.[6] An elevated level VEGF has also been found in the tears of individuals with MGD.[7] These findings have escorted researchers to consider VEGF has a pivotal task for the development of MGD and unsteadiness of the tear film. Anti-VEGF agent, Bevacizumab (Avastin), is a humanized monoclonal antibody that adheres to as well as blocks the biological activity of all the subtypes of VEGF.[8] The present study was carried out with the intention to exhibit the efficiency of injecting Bevacizumab within the meibomian gland for reduction of vascularization of the lid margin and maintain the level of tear film among patients with blepharitis.

Method:

The present study was carried out at Khalid Eye clinic, Karachi from the duration of April 2019 to July 2019. It incorporated eleven patients of either gender with an age range of 20 - 35 years. The study was approved by the Institution Ethics Review Committee and informed consent was taken from each patient. Patients between 20 to 35 years, presence of dryness, sensation of foreign body, burning and watering, MGD with eyelid margin telangiectasia and conformity to follow up visits were included in this study whereas history of injury or surgery to the ocular tissues, eye drop use apart from lubricants, present allergy, infection or inflammation of the ocular tissues apart from MGD, anomaly of the lacrimal system, use of contact lenses, systemic ailment disturbing the surface of ocular tissue and record of contraindication to bevacizumab were excluded. Evaluation of the level of tear film was performed with the help of Schirmer's strip test 2 (without anesthesia) among all the patients by measuring the extent of wetting of Whatman filter paper no. 41 (5 mm wide and 35 mm long). It was placed at the intersection of the central and lateral third of the inferior eyelid making sure it did not come into contact with the cornea or the eyelashes after folding 5mm of one end of the filter paper followed by requesting the patients to close their eyelids and the quantity of wetting of the filter paper was measured and documented from the fold after 5 minutes. Injection Bevacizumab (10 units, 2.5 mg/0.1 mL, 27G needle) was introduced within the meibomian gland through the conjunctiva following aseptic actions. The degree of involvement as well as the severity dictated the number of sites the injection Bevacizumab was applied, which differed between patients, however, the overall dose remaining fixed at 10 units. After application of injection Bevacizumab, a topical antibiotic was instilled. Single ophthalmologist (ZK) performed all the injections. All the patients were followed after one day and one week for post injection inflammatory and infective changes. At one month follow up, the patients were evaluated for the chief conclusion of diminution of eyelid margin vascularization according to literature (Grade 0: No or minimal redness and no telangiectasia formation on the lid margin and Meibomian gland orifices, Grade 1: Only redness and no telangiectasia on the lid margin and Meibomian gland orifices. Grade 2: Redness and telangiectasia involving less than half of lid margin and Meibomian gland orifices, Grade 3: Redness and telangiectasia involving half or more of the lid margin and Meibomian gland orifices)[9] and level of the tear film by Schirmer strip test 2 (without anesthesia).

Result:

This study comprised of eleven patients refractory to previous treatment of blepharitis. Seven (63.6%) patients were females and four (36.4%) were males. The mean age was 27.3 ± 2.9 years. The mean (average) tear film status via Schirmer strip test 2 (without anesthesia) was 8.5 ± 1 mm before injecting Bevacizumab among the patients and 12.5 ± 1 mm after one month of Bevacizumab injection, p value = 0.00 statistical test Paired sample test. Lid margin vascularity was also observed to be noticeably reduced to 1/4th after one month post injection. (Table 1) Subjective complaints by patients of grittiness and foreign body sensation were also reduced. None of the patients in this study developed post injection infection, atrophy or depigmentation at the injection site.

Table 1:

Variables	Pre injection	Post injection
Lid margin vascularity	Grade 3	Grade 1
Tear film level	8.5±1 mm	12.5±1 mm

Discussion:

Blepharitis is a persistent inflammation involving the Meibomian gland dysfunction (MGD)

which can affect both the eyelids, leading to certain pathological changes in the periglandular tissues, evaporation of the tear film, inflammation of the cornea and conjunctiva as well as vascularization of the border of the eyelid.[1,10] Vascularization of the eyelid or telangiectasia occurs often in Blepharitis with MGD owing to an augmented abuse from the UV sun rays which as a consequence result in cellular injury and causing the emission of cytokines related to inflamemation.[11] Unrelenting stimulation of cytokines of inflammation ensues to the liberation of vascular endothelial growth factor (VEGF) with consequent vascularity of eyelid border.[12] Anti-VEGFs have an established part in the management of various disorders of the eye such as proliferative diabetic retinopathy and age-related macular degeneration.[13-15] The use of conventional treatment for blepharitis is proven to be effective but due to the chronic nature of the disease and the failure to remain compliant to the treatment for such a long period of time has led to the resultant chronic debilitating symptoms such as vascularization and scarring of the lid margin.[14,16] A study done by Goyal observed the outcome of the application of intraperitoneal anti-VEGF antibody (400 µg) in a murine model having dryness of ocular surface and showed a noteworthy lessening of inflammatory ocular reaction post injection along with enhancement of the level of the tear film.[17] A different study noticed a decrease in eyelid border vascularization post anti VEGF injection into the meibomian gland, resulting in a maximum effect after 30 days of injection together with an improved TBUT (tear film break up time) seen 30 days post injection.[18] Bevacizumab, an anti VEGF, has been observed to straightforwardly infiltrate through the surface of ocular tissue to neutralize the manufacturing of VEGF and avert the development of vessel formation in the conjunctiva and margin of the lid, having a subsequent circumlocutory effect on the function of the meibomian gland function, concomitantly reducing vascularization of the conjunctiva and the border of the eyelid.[18]

Eyedrop instillation is a preferred technique for curing a disease of the ocular surface but this is only applicable if the medicine has the capability to infiltrate through the epithelial barricade to arrive at the intended tissues contained within a therapeutic range. Owing to Bevacizumab being complete length immunoglobulins with an elevated molecular mass, it is too bulky to make a way into the intact epithelium hence being ineffective as a topical agent.[19] With this knowledge and in accordance with the aforementioned findings, this study was conducted to observe the efficacy of injecting Bevacizumab through the conjunctival side into the meibomian glands. The present study observed a noteworthy diminution in the lid margin vascularization among all eleven patients post 10 units of 2.5 mg/0.1 mL Bevacizumab injection within the meibomian gland through the conjunctiva amid a momentous enhancement in the level of the tear film and a noticeable lessening the symptom of ocular surface with no ensuing adverse effects. The outcome was due to the verity that anti-VEGF agent (Bevacizumab) application within the meibomian gland, disturbed the vicious sequence of MGD by limiting the progression of inflammation and prevented the emission of cytokines with consequent inhibition of meibum accumulation and better discharge of lipids on the surface of the eye through every blink, thereby limiting unnecessary disappearrance of the tear film to preserve the ocular surface and steadiness of the tear film.[18] The current study also observed a superior prevalence of blepharitis among female participants at 63.6% as compared to 36.4% males. Studies done previously has shown that females were extra vulnerable to the dysfunction of the meibomian gland and disorders of the ocular surface due to the effect of sex hormones having a part in the function of the meibomian gland via modifying the manufacturing of lipid.[14,20,21] Male androgens have a shielding consequence on the function of the meibomian gland since estrogen in females promotes a decline in lipid manufacturing and changes the morphology of the meibomian gland.[22,23]

No study has been carried out in this domain to our knowledge observing the effect of application of bevacizumab injection within the meibomian gland on vascularization of the lid margin and level of the tear film. Bevacizumab injection within the meibomian gland gives substantiation that anti VEGF treatment might propose a substitute or adjunctive treatment to the traditional treatment modalities. Additional large scale studies with larger cohorts of participants are required to establish the precise quantity and indications for employment.

Conclusion:

The study showed that injecting Bevacizumab into the meibomian gland is a safe and effective treatment

in terms of reduction of vascularization of the lid margin and improvement in the level of tear film levels among patients afflicted with blepharitis refractory to other treatments.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest

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References:

1. Tsubota K, Yokoi N, Shimazaki J. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. Ocul Surf. 2017 ;15(1):65-76.
2. Jester JV, Parfitt GJ, Brown DJ. Meibomian gland dysfunction: hyperkeratinization or atrophy? BMC Ophthalmol. 2015;15(1):156.
3. Baudouin C, Messmer EM, Aragona P. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. Br J Ophthalmol. 2016;100(3):300-306.
4. Rodr´?guez-Garc´?a A, Gonzalez-God S, Lopez- ´ Rubio S. Blepharokeratoconjunctivitis in childhood: Corneal involvement and visual outcome. Eye (Basingstoke). 2016; 30(3):438-446.
5. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes & cancer. 2011;2(12) :1097-1105.
6. Yoo SA, Kwok SK, Kim WU. Proinflammatory role of vascular endothelial growth factor in the pathogenesis of rheumatoid arthritis: prospects for therapeutic intervention. Mediators of Inflammation. 2008;1(1):1-6.
7. Enriquez-de-Salamanca A, Castellanos E, Stern ME. Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease. Molecular Vision. 2010;16(4):862-873.
8. Tamura, R., Tanaka, T., Miyake, K. Bevacizumab for malignant gliomas: current indications, mechanisms of action and resistance, and markers of response. Brain Tumor Pathol 2017;34(6):62-77.
9. Arita R, Minoura I, Morishige G. Development of definitive and reliable grading scales for Meibomian gland dysfunction. Am J Ophthalmol. 2016;169(12): 125-137.
10. Wei Y, Asbell PA. The core mechanism of dry eye disease is inflammation. Eye Contact Lens. 2014;40 (4):248-256.
11. Chhadva P, Goldhardt R, Galor A. Meibomian Gland Disease: The Role of Gland Dysfunction in Dry Eye Disease. Ophthalmology. 2017;124(11):20-26.
12. Nagineni CN, William A, Cherukuri A, Samuel W, Hooks JJ, Detrick B. Inflammatory cytokines regulate secretion of VEGF and chemokines by human conjunctival fibroblasts: role in dysfunctional tear syndrome. Cytokine. 2016;78(12):16-19.
13. Ba J, Peng RS, Xu D. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. Drug Des Devel Ther. 2015;9(3):5397-5405.
14. Pozarowska D, Pozarowski P. The era of anti-vascular endothelial growth factor (VEGF) drugs in ophthalmology, VEGF and anti-VEGF therapy. Cent Eur J Immunol. 2016;41(3):311-316.
15. Zhang Y, Han Q, Ru Y, Bo Q, Wei RH. Anti-VEGF treatment for myopic choroid neovascularization: from molecular characterization to update on clinical application. Drug Des Devel Ther. 2015;9(2):3413-3421.
16. Hammersmith K. Blepharokeratoconjunctivitis in children. Current Opinion in Ophthalmology. 2015 ;26(4):301-305.
17. Goyal S, Chauhan SK, Dana R. Blockade of prolymphangiogenic vascular endothelial growth factor C in dry eye disease. Arch Ophthalmol. 2012 ;130(12):84-89.
18. Xiaodan J, Yuexin W, Huibin L, Yan L, Mingzhou Z, Xuemin L. Efficacy of intra meibomian gland injection of the anti-VEGF agent bevacizumab for the treatment of meibomian gland dysfunction with lid-margin vascularity. Drug Design, Development and Therapy. 2018;12(4):1269-1279.
19. Al-Debasi T, Al-Bekairy A, Al-Katheri A, Al Harbi S, Mansour M. Topical versus subconjunctival anti-vascular endothelial growth factor therapy (Bevacizumab, Ranibizumab and Aflibercept) for treatment of corneal neovascularization. Saudi Journal of Ophthalmology. 2017;31(2):99-105.
20. Jin X, Lin Z, Liu Y, Lin L, Zhu B. Hormone replacement therapy benefits meibomian gland dysfunction in perimenopausal women. Medicine (Baltimore). 2016;95(31):4268.
21. Tomo Suzuki, Yasuaki Minami, Aoi Komuro, Norihiko Yokoi, Shigeru Kinoshita. Meibomian Gland Physiology in Pre- and Postmenopausal Women. Invest. Ophthalmol. Vis. Sci. 2017;58(2): 763-771.
22. Sahin OG,, Kartal E, Taheri N. Meibomian gland dysfunction: endocrine aspects. ISRN Ophthalmol. 2011;2011:465198.
23. Nanavaty MA, Long M, Malhotra R. Transdermal androgen patches in evaporative dry eye syndrome with androgen deficiency: a pilot study. Br J Ophthalmol. 2014;98(4):567-569.