



SUBCONJUNCTIVAL INJECTION

EFFICACY OF SUBCONJUNCTIVAL INJECTION OF BEVACIZUMAB (AVASTIN) ON CORNEAL NEOVASCULARIZATION IN PATIENTS FOLLOWING KERATOPLASTY

Dr. Faheem Ahmad¹, Dr. Tayyab Mushtaq²

1. MBBS.MCPS.FCPS
Associate Professor
Ophthalmology,
Independent Medical College
Faisalabad.

2. MBBS. FCPS
Assistant Professor Ophthalmology,
Independent Medical College
Faisalabad.

Correspondence Address:

Dr. Faheem Ahmad
MBBS.MCPS.FCPS
Associate Professor Ophthalmology,
Independent Medical College
Faisalabad.
P-79 officer block Muslim Town no 1
Faisalabad.
Doctorfaheem2000 @ yahoo.com

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ABSTRACT... Introduction: Normally the cornea in human eye is crystalline clear membrane present in the anterior most portion of the eyeball. Regarding the various functions of the cornea in human eye it provides protection, clear vision, refractive media the visual system and maintains itself as an immune privileged site. Neovascularization is mostly associated with an inflammation and always indicate a state of disease. Similarly Corneal Neovascularization can cause Graft rejection reaction after keratoplasty the different types of anti-VEGF agents now are used to prevent neovascular eye diseases. These different Anti-VEGF inhibitors are Lucentis, Macugen and bevacizumab/Avastin and used in case of ocular neovascularization. **Objectives:** To determine the efficacy of subconjunctival injection of Avastin on patients having corneal neovascularization following keratoplasty. **Settings:** Department of Ophthalmology Allied Hospital, Faisalabad and Independent University Hospital, Faisalabad. **Study Duration:** The duration of study was 11-02-2015 to 11-07-2015. **Results:** A total of 86 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the efficacy of subconjunctival injection of Avastin on patients having corneal neovascularization following keratoplasty. **Discussion:** Regarding the success of Keratoplasty is determined by many factors especially avascularity of cornea after surgery. Corneal neovascularization is disease process secondary to various ocular insults in which growth of vessels towards central cornea occur from the limbal vascular plexus. But now a days Bevacizumab/Avastin is commonly used in Ophthalmology as "off label" drug in the treatment of Exudative age related macular degeneration as well as in diabetic retinopathy. **Conclusion:** We concluded that the frequency of efficacy of subconjunctival bevacizumab is higher in patients having corneal neovascularization after corneal transplantation.

Key words: Keratoplasty, corneal neovascularization, subconjunctival injection efficacy

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INTRODUCTION

Normally the cornea in human eye is crystalline clear membrane present in the anterior most portion of the eyeball. Regarding the various functions of the cornea in human eye it provides protection, clear vision, refractive media of the visual system and maintains itself as an immune privileged site. Various Ocular insults that include microbial keratitis, immunological conditions, trauma, chemical injury and contact lens wear may cause neovascularization (NV) in cornea.¹

Neovascularization is mostly associated with an inflammation and always indicate a state of disease. However corneal neovascularization is useful in corneal wound healing after injury or in elimination of infection, but it cause reduction

in corneal transparency. Decreased corneal transparency can cause visual acuity deterioration. Similarly Corneal Neovascularization can cause Graft rejection reaction after keratoplasty.²

keratoplasty (corneal transplantation) is usually performed to restore vision. Indications of Keratoplasty includes therapeutic reasons, in corneal ulcers not responding to medical therapy or to improve the structural integrity of cornea secondary to diseases that induced corneal stromal thinning. Various Factors that can affect the success rate of corneal transplantation depend on presence of corneal neovascularization, some pre-existing ocular diseases like glaucoma or dry eyes, type of keratoplasty and effective management of postoperative complications.³

According to various studies, neovascularization in cornea occurs when there imbalance between angiogenic and anti-angiogenic factors and Increased in blood level of angiogenic factors will induced neovascularization in cornea. One of the most common mediators of angiogenesis in cornea is Vascular endothelial growth factor (VEGF) that is up regulated during neovascularization. Different studies proved that Vascular endothelial growth factor (VEGF) is a potent stimulator of endothelial cell growth in vitro and neovascularization in vivo. The Vascular endothelial growth factor can cause neovascularization in other different clinical diseases such as tumors, proliferative diabetic retinopathy, exudative age-related macular degeneration. The different types of anti-VEGF agents now are used to prevent neovascular eye diseases.⁴ These different Anti-VEGF inhibitors are Lucentis, Macugen and bevacizumab/Avastin are used in case of ocular neovascularization.⁵

Regarding Avastin, it is a recombinant humanized monoclonal immunoglobulin antibody specifically directed against human vascular endothelial growth factor (VEGF). While the mechanism of action of Avastin, it binds to soluble VEGF molecules that leads to prevention of its receptor binding capacity that finally inhibits endothelial cell proliferation and vessel formation.⁶

Regarding the use of subconjunctival bevacizumab in terms of regression of corneal neovascularization is controversial in literature. So, this study is conducted to evaluate the efficacy of subconjunctival bevacizumab in regressing the corneal neovascularization to reduce the risk of corneal graft rejection following keratoplasty as well as making transparent cornea after keratoplasty.

OBJECTIVE

The main purpose of this study was to:
To find out the efficacy of subconjunctival injection of Avastin in patients that developed neovascularization in cornea after Keratoplasty.

MATERIAL AND METHODS

Study Design:

Descriptive case series.

Settings

Department of Ophthalmology Allied Hospital, Faisalabad and Independent University Hospital, Faisalabad.

Study Duration:

The duration of study was 11-02-2015 to 11-07-2015.

Sample Size

The total number of patients in this study was 86.

Sampling Technique

Non Probability, Consecutive sampling.

SAMPLE SELECTION

Inclusion Criteria

Patients having age range of 35-65 years of both gender and Patients with corneal neovascularization after Keratoplasty were included in this study.

Exclusion Criteria

Patients having history of use of contact lens, a thromboembolic event, corticosteroid, antithrombotic drugs or aspirin, uncontrolled hypertension or diabetes mellitus were not included in study.

Data Collection Methods

After the approval of hospital ethical committee, patients coming through the OPD of the eye department who fulfilled the inclusion criteria were enrolled and informed consent was taken from all patients.

In Keratoplasty diseased cornea is replaced by healthy donor corneal tissue. Keratoplasty may be full thickness or partial thickness. The full-thickness Keratoplasty is the most commonly performed method as compared to partial thickness Keratoplasty in most of cases. In full-thickness Keratoplasty topical, local, or general anesthesia can be used depending on Surgeon preference. In this study all patients underwent full thickness Keratoplasty under local anesthesia. Subconjunctival avastin of dose of 2.5 mg/0.1

ml per affected quadrant was injected at the area of new vessels formation in those patients that developed corneal neovascularization after Keratoplasty. For assessing the regression of corneal neovascularization and improved corneal transparency after 6 months of treatment complete slit lamp examination with photo documentation was performed. During the Postoperative time all patients were advised topical antibiotics, Lubricants and steroids eye drops. Regular follow up first after two weeks, then on monthly basis for six months after injection was done of all patients and all the information was collected on Performa. Data analysis was performed by SPSS version 16. Mean±Standard deviation was calculated for all quantitative variables. P-value < 0.05 was taken as significant.

RESULTS

A total of 86 cases fulfilling the inclusion/exclusion criteria were enrolled in this study. The subconjunctival injection of Avastin was used in these patients that developed corneal neovascularization after keratoplasty.

Patients were distributed according to age showing that 75.58% (n=65) were between 35-50 years while 24.42% (n=21) were between 51-65 years of age, mean±sd was calculated as 45.63±7.10 years. (Table-I)

72.09% (n=62) were male and 27.91% (n=24) were females according to Gender distribution the patients. (Table-II)

In these patients 82.56% (n=71) frequency of efficacy of subconjunctival injection of avastin was recorded in patients that developed corneal neovascularization after keratoplasty while no efficacy was recorded in 17.44% (n=15) cases. (Table-III)

Stratification for age shows that out of 71 effectively treated cases, 53 were between 35-50 years and 18 were between 51-65 years of age, p value was calculated as 0.75. (Table-IV)

Stratification for gender shows that 59 were male

and 21 were females out of 71 effectively treated cases. (Table-V)

Age(in years)	No. of patients	Percentage
35-50	65	75.58
51-65	21	24.42
Total	86	100
Mean±sd	45.63±7.10	

Table-I. Age distribution (n=86)

Gender	No. of patients	Percentage
Male	62	72.09
Female	24	27.91
Total	86	100

Table-II. Gender distribution (n=86)

Efficacy	No. of patients	Percentage
Yes	71	82.56
No	15	17.44
Total	86	100

Table-III. Frequency of efficacy of subconjunctival injection of avastin on patients having corneal neovascularization following keratoplasty (n=86)

Age	Efficacy (n=71)		P value
	Yes	No	
35-50	53	12	0.75
51-65	18	3	

Table-IV. Stratification for efficacy of subconjunctival injection of avastin on patients having corneal neovascularization following keratoplasty with regards to age (n=86)

Gender	Efficacy (n=71)		P value
	Yes	No	
Male	59	62	0.000
Female	21	3	

Table-V. Stratification for efficacy of subconjunctival injection of avastin on patients having corneal neovascularization following keratoplasty with regards to gender (n=86)

DISCUSSION

The success of Keratoplasty is determined by many factors especially avascularity of cornea

after surgery. Corneal neovascularization is disease process secondary to various ocular insults in which growth of vessels towards central cornea occur from the limbal vascular plexus. The cause of this Corneal neovascularization is secondary to chronic reduction of oxygen in the cornea. The Bevacizumab/Avastin is currently recommended for the treatment of various types of carcinoma in body like colorectal carcinoma, renal carcinoma, lung carcinoma, and mamma carcinoma .But now a days Bevacizumab/Avastin is commonly used in Ophthalmology as “off label” drug in the treatment of Exudative age related macular degeneration as well as in diabetic retinopathy.

However our study was planned regarding the use of subconjunctival bevacizumab in terms of regression of corneal neovascularization after Keratoplasty. So, this study was conducted to evaluate the efficacy of subconjunctival bevacizumab to reduce the risk of corneal graft rejection following keratoplasty by regressing the corneal neovascularization and making cornea transparent after keratoplasty.

In our study, out of 86 cases, 75.58%(n=65) were between 35-50 years while 24.42%(n=21) were between 51-65 years of age, mean \pm sd was calculated as 45.63 \pm 7.10 years, 72.09% (n=62) were male and 27.91% (n=24) were females, frequency of efficacy of subconjunctival injection of avastin on patients having corneal neovascularization following keratoplasty was recorded in 82.56% (n=71) of the cases while 17.44% (n=15) had no findings of efficacy. The findings of our study are same as shown by study of Vasileva Pi et al that showing that corneal transparency in 85.7% patients.⁷ However, In another study regression of corneal neovascularization was observed in 66.7% (8/12 patients).⁸ So findings this study not match with our study.

Koenig et al conducted study of bevacizumab on 30 eyes of 27 patients who were not improving by commonly used anti-inflammatory drugs. They reported that a 61% reduction observed in area of corneal neovascularization and reduction

in vessel diameter was 24% in these patients.⁹ Another study recommended that maximal effects of bevacizumab for reduction of corneal neovascularization observed when this drug was used early in the course of disease.¹⁰

Other human study conducted by Kim SW, Ha BJ, Kim EK also reported the efficacy of bevacizumab in reducing abnormal corneal vessels.¹¹

Dastjerdi et al conducted a study in 2009 on 10 eyes from 10 patients. .After the treatment with bevacizumab these patients presented with clinically stable neovascularization. At end of study Dastjerdi et al reported that a 47.1% decrease in mean neovascular area (p= 0.0014) and a 54.1% decrease in vessel caliber (p = 0.00009) was noted in all such patients.¹²

Subconjunctival bevacizumab therapy in patients having corneal neovascularization shown good results. Like in a study of Chu et al that conducted study in 2011 on 18 patients with lipid keratopathy secondary to corneal neovascularization. All such patients were injected with injections of subconjunctival bevacizumab on monthly basis for three months. On follow up these patients Chu et al measured the extent, centricity, and percentage of involved corneal surface secondary to neovascularization. They observed that after treatment with bevacizumab all above mentioned parameters of corneal neovascularization and lipid deposition showed significant improvement (all p < 0.05).¹³

Further human study conducted by YOU et al also demonstrate significant reduction in corneal neovascularization after treatment of patients with subconjunctivally injected bevacizumab. They further recommended that higher doses of bevacizumab (5.0 mg vs 2.5 mg) for getting better results in such patients.¹⁴

But Subconjunctival administration of bevacizumab does have its own unique risks. So more studies are conducted for comparing the safety of the Subconjunctiva methods and intraocular administration of bevacizumab before

any conclusions can be drawn.

Some studies have also conducted in such patients by using bevacizumab intraocularly. They injected these patients either by intracameral or by intravitreal route. Finally these recent comparative studies shown that bevacizumab either in form of intravitreal, or intracameral is more effective as compared to subconjunctival administration for decreasing corneal neovascularization. Avisar et al conducted a study in experimental models by administering bevacizumab intravitreal and anterior chamber injection. Finally they concluded that both routes also more excellent for decreasing new vessels in models for up to 10 days. However Mouse strains vary in their response to the administration of anti-VEGF agents most like due to their different genetic make up.¹⁵ As well in models, s corneas with intact epithelium topically applied bevacizumab is not able to penetrate.¹⁶ Therefore, these studies must be replicated in humans.

So, according to our study, the efficacy of subconjunctival injection of bevacizumab on patients having corneal neovascularization following keratoplasty is higher and can be used further in our population.

CONCLUSION

We concluded that the frequency of efficacy of subconjunctival bevacizumab is higher in patients having corneal neovascularization after corneal transplantation. So we recommended the use of subconjunctival bevacizumab to reduce the risk of corneal graft rejection following Keratoplasty by regressing the corneal neovascularization and making cornea transparent after Keratoplasty.

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REFERENCES

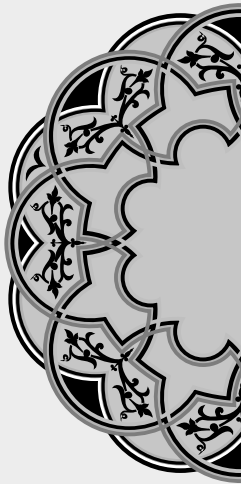
1. Dixon JM. **Corneal vascularization due to corneal contact lenses: the clinical picture.** Trans Am Ophthalmol Soc. 1967; 65:333-40.
2. Bhatti N, Qidwai U, Hussain M, Kazi A. **Efficacy of topical bevacizumab in high risk corneal transplant survival.** Pak J Med Sci. 2013; 29:519-22.
3. Garg P, Krishna PV, Stratis AK, Gopinathan U. **The value**

of corneal transplantation in reducing blindness. Eye. 2005; 19:1106-14.

4. Ozbek Z, Aydin R, Slevier OB, Alper PSM, Saatci AO, Durak I, et al. **Can subconjunctival bevacizumab injection regress corneal neovascularization?** Pak J Ophthalmol.2013; 29:21-5.
5. Wang Q, Yang J, Tang K, Luo L, Wang L, Tian L, et al. **Pharmacological characteristics and efficacy of a novel anti-angiogenic antibody FD006 in corneal neovascularization.** BMC Biotechnol 2014; 14:17.
6. Moisseiev E, Waisbourd M, Ben-Artzi E, Levinger E, Barak A, Daniels T, et al. **Pharmacokinetics of bevacizumab after topical and interavitreal administration in human eyes.** Graefes Arch Clin Exp Phththalmol.
7. Vasileva PI, Hergeldzhieva TG. **Avastin use in high risk corneal transplantation.** Graefes Arch Clin Exp Ophthalmol. . 2002; 2:727-39.
8. Agarwal S, Angayarkanni N, Iyer G, Srinivasan B, Natarajan R, Charola S, et al. **Clinico-biochemical correlation of the effect of subconjunctival bevacizumab for corneal neovascularization.** Cornea. 2003; 4:457-67.
9. Koenig Y, Bock F, Horn F. **Short- and long-term safety profile and efficacy of topical bevacizumab (Avastin) eye drops against corneal neovascularization.** Graefes Arch Clin Exp Ophthalmol.2009; 247:1375-82.
10. Papathanassiou M, Theodossiadis PG, Liarakos VS. **Inhibition of corneal neovascularization by subconjunctival bevacizumab in an animal model.** Am J Ophthalmol. 2008; 145:424-31.
11. Kim SW, Ha BJ, Kim EK. **The effect of topical bevacizumab on corneal neovascularization.** Ophthalmology. 2008; 115:e33-8.
12. Dastjerdi MH, Al-Arfaj KM, Nallasamy N. **Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, non-comparative study.** Arch Ophthalmol.2009; 127:381-9.
13. Chu HS, Hu FR, Yang CM. **Subconjunctival injection of bevacizumab in the treatment of corneal neovascularization associated with lipid deposition.** Cornea. 2011; 30:60-6.
14. You IC, Kang IS, Lee SH. **Therapeutic effect of subconjunctival injection of bevacizumab in the treatment of corneal neovascularization.** Acta Ophthalmol. 2009; 87:653-8.
15. Avisar I, Weinberger D, Kremer I. **Effect of**

subconjunctival and intraocular bevacizumab injections on corneal neovascularization in a model. Curr Eye Res. 2010; 35:108–15.

16. Dastjerdi MH, Sadrai Z, Saban DR. **Corneal penetration of topical and subconjunctival bevacizumab.** Invest Ophthalmol Vis Sci. 2011; 52:8718–23.



*“There are many ways of going forward,
but only one way of standing still.”*

Franklin D. Roosevelt

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Faheem Ahmad	Concept & design, Data collection, Critical expertise & writing, & Final approval	
2	Dr. Tayyab Mushtaq	Concept, Design and Data collection	