

Role of Tetracycline in Corneal Neovascularization

Arshad Ali Lodhi, Murtaza, Munawar Ahmed, Noman Ahmed, Ghulam Haider, Sameen Afzal Junejo, Mustafa Kamal

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See end of article for authors affiliations
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Correspondence to:
Sameen Afzal Junejo
Department of Ophthalmology,
Liaquat University of Medical
and Health Sciences/Jamshoro,
Sindh Pakistan
Email: sameenafzal1@gmail.com

Purpose: To find the efficacy of topical tetracycline in corneal neovascularization.

Material and Methods: In this prospective observational clinical analysis, patients more than fifteen year's age of either sex were enrolled. Anterior segment slit lamp examination was performed. Fluorescein 1% dye and rose bengal were used to stain cornea at the bed and margins simultaneously. The area of corneal vascularization was measured in mm using 0.5% fluorescein dye. The percentage of neovascularized corneal areas to the entire cornea was calculated.

Result: Out of twenty eight patients twenty one completed follow up period of four months. Among 21 patients males were 10 (47.6%), and females 11 (52.38%) with unilateral and bilateral corneal neo-vascularization. 15 (71.42%) responded well and showed reduction in corneal new vessels from 7 mm pre-treatment to 2 mm (overall) post treatment at the end of fourth month. six patient showed poor or no response due to extended fibrosis.

Conclusion: Topical tetracycline has remained quite instrumental in reducing superficial epithelial and sub-epithelial corneal new vessels.

Key Words: Cornea; Neovascularization; Tetracycline; Therapeutic effect.
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Ocular neovascularization is the abnormal growth of blood vessels in the retina, choroid and cornea. They can lead to many complications like fibrosis, scarring and blindness. Common causes of corneal neovascularization are blepharitis, keratitis, corneal graft rejection, chemical injuries and improper or prolonged use of contact lenses.¹ The main source of superficial corneal neovascularization arises from conjunctiva. The superficial vessels adopt the pattern of diffuse tree branches and are usually observed passing through the corneo-scleral junction invading anterior layers of cornea up to substantia propria. While deep corneal vessels are having straight course originate from deep scleral vessels and penetrate the deeper corneal layers including corneal stroma and beyond. Antibiotics, lasers and other treatment have limited approach. Steroids are used to combat with this problem but

extended use can result in to unavoidable side effects and complications.^{1,2}

Tetracycline is a second generation long acting non selective antibiotic.^{2,3} Topical application inhibits corneal lysis, treats corneal ulcers and encourages corneal epithelium healing.^{4,5} Apart from this, tetracycline has also been proved to be quite effective in inhibiting corneal new vessels by inhibiting matrix metalloproteinase (MMP) activity.^{6,7}

Topically induced drugs have become more successful and better effective in the treatment of ocular surface disorders.⁸ Tetracycline or its derivative preparations (doxycycline, minocycline) accelerate corneal wound healing and promote reduction in corneal new vessels by inhibiting MMP activity.^{9,10}

The objective of this study was to document the

therapeutic effect of topical tetracycline on superficial corneal neovascularization.

MATERIAL AND METHODS

This prospective observational clinical analysis was performed at Liaquat University Eye hospital Hyderabad, Sindh of Liaquat University of Medical and Health Sciences / Jamshoro Pakistan from June 2011 to May, 2015.

Inclusion criteria: The subjects of more than fifteen years of age from both genders with unilateral or bilateral superficial (epithelial and sub-epithelial bowman membrane) corneal vascularization associated with ocular surface disorders without any history of ocular surgery were included.

All the enrolled cases were examined at outpatient department of the tertiary eye care center. Detailed history and verbal consent of the patients was obtained. Anterior segment was examined using slit lamp bio-microscope. Corneal staining was done with fluorescein 1% dye. Rose Bengal stains were used to stain devitalized cornea. The area of corneal vascularization was measured in mm by using 0.5% fluorescein under cobalt blue filter on slit lamp bio-microscope by the same ophthalmologist. The percentage of neovascularized corneal areas to the entire cornea was calculated.

The primary treatment of different antibiotics and steroids was stopped. The secondary treatment was started with tetracycline (HCL-USP 5 mg) ophthalmic gel thrice a day. Tetracycline thus used during this study was arranged through a renowned pharmaceutical company.

The area of corneal epithelial defect with new vessels was measured on 15th day, one month and every two months for four months. All the subjects were requested to complete the treatment follow up criteria of this study. Statistical Package of Social Science (SPSS) version 14 was used for statistical data analysis on corneal vascularization.

RESULTS

Out of 28, seven patients did not complete the 4 months follow up and will not be discussed in the results. In twenty one patients who completed follow up, male were 10 (47.6%), female 11 (52.38%) with unilateral and bilateral corneal neo-vascularization were registered for this study (Fig. 1-3). Most of the

subjects belonged to rural areas. The characteristics of enrolled patients is mentioned in table 1.

Seven (25.0%) subjects were lost to follow up. Out of remaining twenty one, there was significant reduction in corneal neo-vascularization in 15 (71.42%) patients.

Table 1: Characteristics of Patients with Corneal Neo-vascularization (n = 21).

Sex	No. of Patient (%)
Male	10 (47.6)
Female	11 (52.40)
Age up to 20 years	02 (9.52)
Up to 30 years	05 (23.8)
Up to 40 years	06 (28.57)
More than 40 years	08 (38.09)
Residency:	
Rural	15 (71.42)
Urbal	06 (28.57)
Socio-economic Status	
Upper	0.0
Middle	06 (28.57)
Lower	15 (71.42)

Table 2: Ocular Diseases with Corneal Neo-vascularization (n = 21).

Associated Disease	No. of Patients	Cor. New Vessels in Mm	% of New Vessels to Cor. Diameter of 11mm over all
Blepharitis	08	4 - 5	40.9
Trichiasis	06	5 - 6	50.0
Kearto conj Sicca	05	6 - 7	59.0
Burn Injury	02	9 - 10	86.3

The student - t test was used to evaluate the data. The mean age of the patients was 39.38 years. The results of treatment were quite significant (2-tailed), with the P value 0.002. Standard deviation was 1.21253; confidence interval of the difference was

95%. The documented overall reduction in new vessels was from 7 mm to 2 mm after four months of treatment (Fig. 4 - 6). One (4.47%) lady recovered moderately and remaining five (23.81%) did not respond to the treatment due to extended fibrosis although the symptoms were relieved.

DISCUSSION

Corneal neovascularization (CNV) is a sight-threatening condition. Most often it develops secondary to inflammatory conditions and ocular surface disorders. Corneal trauma due to chemical burns causes severe corneal neovascularization.¹¹ In this study two patients developed corneal neovascularization after alkali burn, which could not improve in spite of abrupt treatment with tetracycline and associated medications.

Various sources promote neovascularization i.e. growth factors, prostaglandins and interleukins. The process of corneal new vessels formation consists of two steps. First is the vascular endothelial growth factor (VEGF) related to proliferation of vascular endothelium. Second step reformation of extracellular matrix followed by activation of cytokines. Corneal neovascularization due to alkali burns is related to inflammation. In response to a chemical burn the inflammatory cells release cytokines and MMPs. There is also a variety of compounds supposed to inhibit corneal new vessels. Such anti angiogenic factors are non-steroidal anti-inflammatory agents, steroids and immuno suppressives.^{12, 13}

The treatment of choice in corneal neovascularization is topical use of corticosteroids. But due to their disastrous side effects and complications now a days have got restricted application.¹⁴ In our study steroids use was not documented in any registered subject.

The efficacy of tetracycline depends upon its concentration, route of application, and patient's acceptance. The recommended dosage of tetracycline is absolutely non-toxic to the corneal surface and adnexa. In our study tetracycline with the dosage of 5 mg was used topically three times a day. Its effect on cornea is biological oriented rather than antimicrobial. According to the recent global research, tetracycline also acts to suppress tumor growth, angiogenesis, resorption of bone.^{15, 16}

Limitations to This Study

In our area not much work has yet been done on this

issue. We could not compare the results of our study with other national studies. There is no doubt a need for advanced study and research on the efficacy of tetracycline in different ocular diseases particularly corneal neovascularization.

CONCLUSION

Tetracycline has proved itself to be more promising in preventing and reducing superficial corneal neovascularization thus enhancing the inhibitory effects of angiogenesis.

Author's Affiliation

Dr. Arshad Ali Lodhi
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Murtaza
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Munawar Ahmed
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Noman Ahmed
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Ghulam Haider
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Sameen Afzal Junejo
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Dr. Mustafa Kamal
Department of Ophthalmology
Liaquat University of Medical and Health Sciences/Jamshoro, Sindh/Pakistan

Role of Authors

Dr. Arshad Ali Lodhi
Drafting, methodology, patient's selection, and literature search.

Dr. Murtaza

Maintained the post treatment follow up record of all the subjects who full filed regular follow up criteria of this study.

Dr. Munawar Ahmed

Drafting, methodology, patient's selection, and literature search.

Dr. Noman Ahmed

Performing ocular examinations and data collection.

Dr. Ghulam Haider

Performing ocular examinations and data collection.

Dr. Sameen Afzal Junejo

Selection of patients, examination treatment and follow-up.

Dr. Mustafa Kamal

Maintained the post treatment follow up record of all the subjects who full filed regular follow up criteria of this study.

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