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Original Research Paper

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ROLE OF TETRACYCLINE IN CORNEAL NEOVASCULARIZATION

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ABSTRACT

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.

KEYWORDS : Cornea; Neovascularization; Tetracycline; Therapeutic effect.

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. 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 Deptt of Ophthalmology Govt Medical College Sgr from June 2019 to June, 2022.

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 biomicroscope. 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 biomicroscope 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. 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) 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.

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.

Table 1:Characteristics of patients with corneal neo-vascularisation (n=21)

Sex	No.of patients(%)
Male	10(47.6)
Female	11(52.40)
Age Up to 20 years	2(9.52)
Up to 30 years	05(28.3)

Up to 40 years	06(28.57)
Ø 40 years	08(38.09)
Residence	
Rural	15(71.42)
Urban	06(28.57)
Socio-economic Status	
Upper	0.0
Middle	06(28.57)
Lower	15(71.42)

Table:2 Ocular Diseases With Corneal Neo-vascularisation(n=21)

Associated Disease	No. of Patients	Corneal new vessels in mm	%of new vessels to corneal dia of 11mm
Blepharitis	08	4-5	40.9
Trichiasis	06	5-6	50.0
KCS	05	6-7	59.0
Burn Injury	02	9-10	86.3

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 neova scularization after alkali burn, which could not improve inspite 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] .

CONCLUSION

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

REFERENCES

1. Lim P, Fuchsluger TA, Jurkunas UV. "Limbal stem cell deficiency and corneal neovascularization", Semin Ophthalmol. 2000; 24: 139-48.
2. Moses MA, Harper J, Folkman J. "Doxycycline treatment for lymphangio leiomyomatosis with urinary monitoring for MMPs," N Engl J Med. 2006; 354: 2621–2.
3. Lindeman JH, Abdul-Hussien H, van Bockel JH, et al. Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells, "Circulation. 2009; 119: 2209–16.
4. Villarreal FJ, Griffin M, Omens J, Dillmann W, Nguyen J, Covell J. Early short-term treatment with doxycycline modulates postinfarction left ventricular remodeling, Circulation. 2003; 108: 1487–92.
5. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review, Cornea. 2000; 19: 274–7.
6. Dan L, Shi-long Y, Miao-li L, Yong-ping L, Hong-jie M, Ying Z, Xiang-gui W. "Inhibitory effect of oraldoxycycline on neovascularization in a rat corneal alkali burn model of angiogenesis, "Curr Eye Res. 2008; 33: 653–60.
7. Cox CA, Amaral J, Salloum R, Guedez L, Reid TW, Jaworski C, John-Aryankalayil M, Freedman KA, Campos MM, Martinez A, Becerra SP, Carper DA. Doxycycline's effect on ocular angiogenesis: an in vivo analysis. Ophthalmology. 2010; 117: 1782–91.
8. Samtani S, Amaral J, Campos MM, Fariss RN, Becerra SP. Doxycycline-mediated inhibition of choroidal neovascularization, Invest Ophthalmol Vis Sci. 2009; 50: 5098–5106.
9. Anumolu SS, DeSantis AS, Menjoge AR, Hahn RA, Beloni JA, Gordon MK, Sinko PJ. Doxycycline loaded poly (ethylene glycol) hydrogels for healing vesicantinduced ocular wounds. Biomaterials. 2010; 31: 964–74.
10. Su W, Li Z, Lin M, et al. The effect of doxycycline temperature-sensitive hydrogel on inhibiting the corneal neovascularization induced by bFGF in rats. Graefes Arch Clin Exp Ophthalmol. 2011; 249: 421–7.
11. Wagoner MD. Chemical injuries of the eye: current concepts in pathophysiology and therapy, Surv Ophthalmol. 1997; 41: 275–313.
12. Li T, Hu A, Li S, Luo Y, Huang J, Yu H, Ma W, Pan J, Zhong Q, Yang J, Wu J, Tang S. KH906, a recombinant human VEGF receptor fusion protein, is a new effective topical treatment for corneal neovascularization," Mol Vis. 2011; 17: 797–803.
13. Ma DH, Chen JK, Kim WS, Hao YX, Wu HC, et al. "Expression of matrix metalloproteinases 2 and 9 and tissue inhibitors of metalloproteinase 1 and 2 in inflammation-induced corneal neovascularization, Ophthalmic Res. 2001; 33: 353–62.
14. De Paiva CS, Corrales RM, Villarreal AL, Farley WJ, Li DQ, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye," Exp Eye Res. 2006; 83: 526–35.
15. Federici TJ. The non-antibiotic properties of tetracyclines: Clinical potential in ophthalmic disease. Pharmacol Res. 2011; 64: 614–23.
16. Liang D, Yan SL, Lin ML, Li YP, Ma HJ, et al. Inhibitory effect of oral doxycycline on neovascularization in a rat corneal alkali burn model of angiogenesis. Curr Eye Res. 2008; 33: 653–60.