The principal goals of such therapy are to increase corneal rigidity, enhance the corneal integrity and mechanical strength. Therefore, it is possible to halt keratoconus progression using UVA at 370nm and the photosensitizer riboflavin stiffening the collagen matrix of the cornea. Riboflavin, administered topically to de-epithelialized corneas, serves as photosensitizer that is activated by UVA to induce crosslinking of collagen fibrils. With the aid of this new approach, stromal fiber photopolymerization is achieved through the development of strong chemical bonds between collagen fibrils. With the aid of this new approach, stromal fiber photopolymerization is achieved through the development of strong chemical bonds between collagen fibrils.

**INTRODUCTION**

Keratoconus is a non-inflammatory, degenerative disorder distinguished by paracentral corneal thinning and secondary ectasia resulting in irregular astigmatism, severe myopia which lead to progressive impairment of vision.

Progressive keratoconus is defined as one of the following changes over 12 months:

- An increase of 1.00 diopter (D) or more in the steepest K value,
- An increase of 1.00 diopter or more in manifest cylinder.

The prevalence of keratoconus varies considerably according to ethnic and regional factors, ranging from 50 and 600 in 1,00,000 individuals in the general population, its incidence rate is 1 to 2 in 1,00,000 individual. The onset is typically at puberty with progression of disease for 10-20 years when it tends to stabilize.

Its etiology is not understood and includes genetic, biochemical and physical factors. It usually appears as an isolate condition but has been associated with number of ocular and systemic disorders including vernal disease, retinitis pigmentosa, atopy, blue sclera, magnesium deficiency, Down’s syndrome, connective tissue disorders like Marfans syndrome, Ehler Danlos syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum.

Management of keratoconus depends on their severity and the extent of irregular astigmatism. Mild cases are correctible with spectacles and soft toric contact lenses. However, with the progressive disease, the cornea becomes more irregular and rigid, gas permeable lenses are required. In 15-20 percent of keratoconic patients, surgery, typically penetrator keratoplasty becomes necessary as a result of contact lens intolerance, corneal scarring and thinning. Corneal collagen crosslinking enhances the mechanical strength and biochemical stability of the cornea and is the only treatment to date that addresses the pathophysiology of Keratoconus.

Crosslinking is performed by using UVA and the photosensitizer riboflavin stiffening the collagen matrix of the cornea. Riboflavin, administered topically to de-epithelialized corneas, serves as photosensitizer that is activated by UVA light. The light induced production of oxygen radicals lead to the development of strong chemical bonds between collagen fibrils. With the aid of this new approach, stromal fiber photopolymerization enhances the corneal integrity and mechanical strength. Therefore, it may be considered as halting keratoclasia progression during the progressive phase of keratoconus.

The principal goals of such therapy are to increase corneal rigidity, stabilize its refractive and biomechanical properties and thus improve vision. In contrast, modern therapies such as rigid contact lenses, intracorneal rings, photorefractive keratectomy or epikeratoplasty can be used only to correct refractive errors of the disease rather than to stop the keratoconus progression.

**ABSTRACT**

**PURPOSE** To evaluate outcomes of collagen crosslinking in patients having progressive keratoconus.

**METHODS** A prospective study was done in eyes that underwent corneal collagen crosslinking for treatment of progressive keratoconus. This study was performed after approval from Institutional Ethics Committee and informed consent was obtained from all the patients. Data was analyzed using JASP 0.8.3.1 and MS-Excel 2013.

**RESULT** The mean age was 20.94 ± 2.04 years, 21 (63.63%) were males, 12 (36.36%) were females. The mean uncorrected visual acuity (UCVA) pre-operative and post-operative at 6 months were 0.64 ± 0.37 and 0.53 ± 0.31 (logMAR) respectively (p value 0.03). Mean spherical equivalent pre-operatively and post-operatively at 6 months were -2.85 ± 2.14 and -2.38 ± 1.70 respectively (p < 0.001). Mean keratometry (Mean K) pre-operative and post-operative were 49.85 ± 4.10 Dioptres (D) and 49.22 ± 4.90 D respectively (p = 0.0007).

**CONCLUSION** Corneal collagen crosslinking with UV-A and riboflavin is a safe and effective method for halting the deterioration of progressive keratoconus.

**KEYWORDS**

Riboflavin, Logmar, Beva, Keratometry, Crosslinking, Collagen, Keratoconus, Ultraviolet.

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**METHODOLOGY**

It was a prospective, hospital based study in 39 eyes that underwent corneal collagen crosslinking for treatment of progressive keratoconus in Mahatme Eye Bank and Eye hospital, Nagpur from August 2017 to October 2018. This study was performed after approval from Institutional ethics committee and considering the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients.

Inclusion criteria were Age - more than 18 years of age, progressive keratoconus with one of the changes over 12 months such as an increase of 1.00 diopter (D) or more in the steepest K value or an increase of 1.00 diopter or more in manifest cylinder. In the corneal stroma, collagen vascular diseases, Active ophthalmic inflammation, History of herpetic keratitis, Current corneal infection, Pregnancy and lactation, Severe dry eye, Autoimmune diseases and patients with previous ocular surgeries were excluded.

Demographic data of patients was collected including name, age, sex, occupation and personal details. Detailed history of patients complaining of diminution of vision was taken including duration and relevant past history. Secondary causes of diminution of vision were identified.

A baseline ophthalmic examination was performed on all eyes, which included slit lamp biomicroscopy, ultrasonic corneal pachymetry, and simultaneous measurement of corneal tomography and Scheimpflug camera-based corneal topography.

Snellen visual acuity was converted to the corresponding logarithm of the minimum angle of resolution (logMAR) value using standard conversion tables for the purpose of statistical analysis. All
measurements was obtained by an experienced operator using the same machines and procedures.

Uncorrected visual acuity. Best corrected visual acuity, Spherical equivalent, mean keratometry reading (from topography) and Central corneal thickness were evaluated.

Patients were followed for a period of 6 months.

Collagen crosslinking was performed under topical anaesthesia (paracaine) before procedure. Topical steroid (Prednisolone acetate 1% eye drops) and antibiotic (moxifloxacin 0.5% eye drops) four times daily for one week; steroid tapered to three times/day for the next week and then two times/day for the next 2 weeks and lacrimal substitutes (preservative-free artificial tears) four times daily for 4-6 weeks were the post-operative treatment given.

Data analysis was done with the help of JASP 0.8.3.1 and MS-Excel 2013. Descriptive statistics such as mean, standard deviation (SD), 95% confidence intervals (CI) were analyzed. Wilcoxon Signed Rank test was used. P value less than 0.05 was considered significant.

RESULT

In this study, age of the patients were ranging from 18 to 26 years with mean age being 20 ± 2.06 (SD) years. 63.63% of the total cases were males and 36.36% were females.

Table 1: Age distribution among study cases

| Age group (Yrs) | No. of patients | Percentage (%) |
|----------------|----------------|----------------|
| 18             | 01             | 03.03          |
| 19             | 12             | 36.36          |
| 20             | 07             | 21.21          |
| 21             | 05             | 15.15          |
| 22             | 06             | 18.18          |
| 23             | 02             | 05.12          |
| 24             | 03             | 09.09          |
| 25             | 02             | 05.12          |
| 26             | 01             | 03.03          |

The above table 1 shows that 36.36% of patients were belonged to 19 years of age followed by 21% of 20 years of age.

Mean spherical equivalent (SE) of 19 patients remained stable (48.71 %) and decreased in 18 eyes (46.15%). Mean spherical equivalent pre-operatively and post-operatively at 6 months were -2.85 ± 2.14 (SD) and -2.38 ± 1.70 (SD) respectively.

Mean uncorrected visual acuity (UCVA) pre-operative and post-operative at 6 months were 0.64 ± 0.37 and 0.53 ± 0.31 (logMAR) respectively (p value 0.03).

The mean pre-operative and post-operative best corrected visual acuity (BCVA) at 6 months were 0.31 ± 0.29 and 0.19 ± 0.20 (logMAR) respectively. Amongst 39 eyes, one line improvement was evident in 7 eyes (17.94%); two lines improvement in 10 eyes (25.64%); three lines improvement in 2 eyes (5.13%). Also, keratoconus worsened in one eye (2.56%).

Similarly, in a study conducted on 38 eyes by Vinciguerra et al in 2010, mean BCVA (logMAR) increased from 0.16 ± 0.14 preoperatively to 0.06 ± 0.08 postoperatively (p value <0.05). In a study conducted by Hashemi et al, mean BCVA (logMAR) pre-operative and post-operative were 0.31 ± 0.28 and 0.19 ± 0.20 respectively.

The present study results depicted the mean pre-operative and post-operative best corrected visual acuity (BCVA) at 6 months were 0.31 ± 0.29 and 0.19 ± 0.20 (logMAR) respectively and were found to be statistically significant (p value<0.001). Amongst 39 eyes, one line improvement was evident in 7 eyes (17.94%); two lines improvement in 10 eyes (25.64%); three lines improvement in 2 eyes (5.13%). Also, keratoconus worsened in one eye (2.56%).

DISCUSSION

In this study, we compared the efficacy in the form of topographic (Mean keratometry), refractive (spherical equivalent) and visual outcomes (uncorrected and best corrected visual acuity). Patients were followed up to 6 months and results were then analysed. We had a total of 39 eyes of 33 patients.

In our study, we noted that patients were of age 18 to 26 years, mean age was 20.94 ± 2.04 years. 36.36% of patients belonged to 19 years of age followed by 21.21% of 20 years of age. The study done by Tiveron Jr et al and Agrawal et al, reported that the mean age of the patients were 19 ± 5.61 years and 16.9 ± 3.5 years respectively. Our study was in concordance with these studies. This concluded that keratoconus occurs in younger population.

In present study, the mean uncorrected visual acuity (UCVA) pre-operative and post-operative at 6 months were 0.64 ± 0.37 and 0.53 ± 0.31 (logMAR) respectively (p value 0.03). In a study by Henriquez et al, mean pre-operative and post-operative UCVA were 1.18 ± 0.80 and 0.46 ± 0.36 (logMAR) respectively (p< 0.001). Another study, conducted by Vinciguerra et al in 2012, found that mean UCVA pre-operative and post-operative were 0.79 ± 0.21 and 0.58 ± 0.18 (LogMAR) (p < 0.05). Our findings were in concordance with the studies done by both Henriquez et al and Vinciguerra et al.

In a study conducted by O Brart et al, evaluated 30 eyes in 2013. They noted that mean spherical equivalent pre-operative and post-operative were -1.61 ± 1.97 and -2.38 ± 1.70 respectively (p < 0.001). A study conducted by Vinciguerra et al in 2009, noted mean spherical equivalent pre-operative and post-operative was -3.63 ± 3.45 and 2.06 ± 2.21 respectively; the difference between them was statistically significant (p=0.03).

O Brart et al, evaluated 30 eyes in 2013. They noted that mean spherical equivalent pre-operative and post-operative was -1.61 ± 1.97 and -2.38 ± 1.70 respectively (p < 0.001). A study conducted by Vinciguerra et al, found that mean K decreased from 50.37 D pre-operative to 49.02 D post-operative which when compared were statistically significant (p = 0.03). In a study conducted by O Brart et al, mean K pre-operative and post-operative were 46.44± 3.4 D and 45.6 ± 3.3D respectively. These when compared were statistically significant (p value <0.001). Ivarsen et al in 2013, noted that mean K pre-operative and post-operative were 61.2 ± 3.7 D and 59.1 ± 3.7 D and were found statistically significant when compared with each other. Our results were comparable with the studies conducted by O’Brart et al, Vinciguerra et al and Ivarsen et al.

We inferred that there is a significant reduction of mean keratometry at 6 post-operative months.

In this study, Mean keratometry (mean K) pre-operative and post-operative were 49.85 ± 4.10 Diopters (D) and 49.22 ± 4.09 D respectively (p = 0.0007). We also noted that, there were 34 stable eyes (87.17 %) post corneal collagen crosslinking and remained in the same preoperative mean K class. Mean K decreased in about 4 eyes (10.25 %). These results demonstrate a flattening effect of crosslinking on keratoconic eyes. A study by Vinciguerra et al, found that mean K decreased from 50.37 D pre-operative to 49.02 D post-operative which when compared were statistically significant (p=0.03).

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decreased significantly to 470 ± 29.01 microns from pre-operative 490.68 ±30.69 microns (p<0.05). Our results were in concordance with the study conducted by Vinegguera et al. We concluded that the mean CCT decreased significantly at 6 post-operative months.

In this study, we did not come across any complications related to corneal collagen crosslinking like sterile or infective keratitis, corneal haze etc.

**CONCLUSION**

We conclude that 87.17% of progressive Keratoconus patients achieved stabilization of mean keratometry after corneal collagen crosslinking with UV-A and Riboflavin. Also, there was statistical improvement in visual function [preoperative BCVA 0.31 ± 0.29 improving to 0.19 ± 0.20 (logMAR) postoperatively]. Corneal collagen crosslinking with UV-A and riboflavin is a safe and effective method for halting the deterioration of progressive keratoconus.

**RECOMMENDATION**

Corneal collagen crosslinking is the standard treatment to arrest the progression of keratoconic eyes. The stabilization of keratoconus in this study underscores the importance of early diagnosis in progressive cases.

**CONFLICT OF INTEREST- No**

**REFERENCE**

1. Dengue and severe dengue. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue. (Last accessed on 08.02.2020).
2. Mitra S, Gautam J, Jambugalam M, Abhilash KP, Jayaseelan V. Clinical score to differentiate scrub typhus and dengue: A tool to differentiate scrub typhus and dengue. Journal of global infectious diseases. 2017 Jan;9(1):12. (Last accessed on 09.02.2020).
3. Koshy M, Mishra AK, Agrawal B, Kunup AR, Hansdak SG. Dengue fever complicated by hemophagocytosis. Oxford medical case reports. 2016 Jun 1;2016(6):121-4. (Last accessed on 19.02.2020).
4. Gubler, D. J. 1988. Dengue, p. 223–260. In T. P. Monath (ed.), Epidemiology of arthropod-borne viral diseases. CRC Press, Inc., Boca Raton, Fla. (Last accessed on 10.02.2020).
5. Anonymous. 1986. Dengue hemorrhagic fever, diagnosis, treatment and control. World Health Organization, Geneva, Switzerland. (Last accessed on 09.02.2020).
6. Hayes, E. B., and D. J. Gubler. 1992. Dengue and dengue hemorrhagic fever. Pediatr. Infect. Dis. J. 11:311–317. (Last accessed on 08.02.2020).
7. Siler, J. F., M. W. Hall, and A. Hitchens. 1926. Dengue, its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity and prevention. Philipp. J. Sci. 29:1–304. (Last accessed on 19.02.2020).
8. Simmons CP, Farrar JJ, Nguyen v V, Wills B. Dengue. N Engl J Med. 2012 Apr 12;366(15):1423-32. (Last accessed on 09.02.2020).
9. Huang H-W, Tseng H-C, Lee C-H, Chuang H-Y, Lin S-H. Clinical significance of skin rash in dengue fever: A focus on discomfort, complications, and disease outcome. Asian Pac J Trop Med 2016; 9(7): 713–8. (Last accessed on 10.02.2020).
10. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL et.al. The global distribution and burden of dengue. Nature; 496:504-507. (Last accessed on 09.02.2020).
11. Brady OJ, Gething PW, Bhattacharya S, Wiwanitkit V, Aboyans V, Tatem AJ et.al. The global burden of dengue virus infection: The effect of latent dengue virus infections on the global distribution of dengue. Nature; 509:629–634. (Last accessed on 19.02.2020).
12. Waterman SH, Gubler DJ. Dengue fever: Clin Infect Dis. 1989;7:117–22. (Last accessed on 19.02.2020).
13. Thomas TA, John M, Kanish B. Mucocutaneous manifestations of dengue fever. Indian journal of dermatology. 2010 Jan;55(1):79. (Last accessed on 09.02.2020).