Intraocular Pressure Measurements After Corneal Collagen Crosslinking With Riboflavin and Ultraviolet A in Eyes with Keratoconus

Sohel Mahmud[1], Soheb Ahmed Robin[2], Nahal Mostak Khan[3], Lutfullahil Khabir[4], Bipul Kumer De Sarker[5], Golam Mohaimen Chowdhury[6]

Abstract

For the treatment of corneal ectasias such as keratoconus, corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A irradiation has recently been developed. Intraocular pressure (IOP) measurements may be affected by an increase in corneal stiffness brought on by CXL. Our research sought to ascertain if corneal collagen crosslinking with UVA and riboflavin would have an impact on intraocular pressure readings using Goldmann applanation tonometry (GAT). The investigation was conducted at the Ispahani Islamia Eye Institute and Hospital's cornea department in Dhaka. In this study, 31 eyes from 30 patients receiving CXL treatment because to keratoconus were enrolled. All of the patients had a thorough ocular examination at the time of their initial registration. IOP measured one month, three months, and six months following CXL using Goldmann applanation tonometry. Thirty patients were included, of which over one third (36.7%) were under the age of fifteen. The age ranged from 11 to 27 years old, with a mean of 18.0±4.4 years. The majority was male (86.7%). The gender ratio was 6.5 to 1. The intraocular pressure was 10.03±2.09 mmHg prior to CXL, 11.23±1.86 mmHg in the first month following CXL, 12.42±1.86 mmHg in the third month following CXL, and 12.94±1.98 mmHg in the sixth month following CXL. When compared to before CXL, the mean intraocular pressure increased at the one-month, three-month, and six-month marks. These increases were statistically significant ($p<0.05$). In eyes with keratoconus, riboflavin-UVA CXL resulted in a substantial increase in intraocular pressure as determined by GAT. This increase was likely caused by an increase in corneal stiffness. This suggests that routinely measuring IOP may be a reliable and significant predictor of rising corneal resistance, which is the primary objective of CXL treatment.

Keywords: *Intraocular pressure measurements, Corneal Collagen Crosslinking, Riboflavin, Ultraviolet A, Eyes, Keratoconus*

Introduction

Keratoconus is a non-inflammatory, bilateral condition that causes the cornea to gradually thin and bulge, taking on a conical form. This condition impairs visual acuity and causes uneven astigmatism [1, 2]. The geographic location, diagnostic criteria, and patient cohort all have a significant impact on the reported prevalence of keratoconus. Studies have shown that the prevalence might vary from 0.3 per 100,000 in Russia to 2300 per 100,000 (0.0003%-2.3%) in Central India. The large range in occurrence could be attributed to environmental factors. Locations

1. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; sohel_sumon7070@yahoo.com
2. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; ahamedsoheb@gmail.com
3. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; drmostaknio@gmail.com
4. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; shiblynio15@gmail.com
5. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; drbipul26@gmail.com
6. Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; gmchowdhury123@gmail.com

Address of Correspondence: Sohel Mahmud, Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh; sohel_sumon7070@yahoo.com

with warmer temperatures and more sunlight, like the Middle East and India, are more common than places with colder temperatures and less sunlight, such Finland, Denmark, Minnesota, Japan, and Russia. The disparities in the reported prevalence of keratoconus may be explained by ethnic variances. Two surveys conducted in the UK revealed that Asian (Bangladeshi, Pakistani, and Indian) respondents had a prevalence that was 4.4 and 7.5 times higher than that of white Caucasians [3].

Increased degradative enzyme activity and a decrease in enzyme inhibitors are linked to stromal thinning and Bowman's layer loss in keratoconus. Reduced amounts of sulphated proteoglycan and total protein, as well as decreased collagen cross-linking and fluctuating total collagen content, are observed in keratoconic corneas [4]. In comparison to normal corneas, 60% of keratoconic corneas exhibit apoptotic stromal keratocytes along with indications of increased oxidative damage, which ultimately results in reduced cell viability and cell death. The stromal lamellae of keratoconic corneas are irregularly distributed and intrude transversely into the Bowman's layer. Another theory is that this can cause corneal lamellar slippage and stretching.1. When conservative measures to treat keratoconus fail, lamellar or penetrating keratoplasty may be used [2, 5]. Other therapeutic options for keratoconus include intrastromal corneal ring segments, contact lenses, and spectacles.

Recently, riboflavin (vitamin B2) and ultraviolet A (UVA) irradiation have been used to create corneal collagen cross-linking (CXL), a unique therapeutic option for the treatment of corneal ectasia, including keratoconus [6]. It is believed to function by improving the tissue's biomechanical characteristics and resistance to enzymatic digestion [7, 8]. When applied topically to depithelialized corneas, riboflavin functions as a photosensitizer that is triggered by ultraviolet A radiation. The generation of oxygen radicals by light causes collagen fibrils to form strong chemical connections with one another, hardening the cornea as a result [9]. Preventing progression is one of the main benefits of CXL. Treatment options other than cross-linking were insufficient to turn a progressing illness into keratoconus. Recurrence of karatoconus may happen even after corneal transplantation. The process of collegen cross-linking is easy to follow [10].

Compared to corneal transplantation or corneal intrastromal ring segment implantation, the collagen cross-linking learning curve is far less important. After cross-linking, the recuperation phase is brief [11]. There are no major side effects from the extraocular collagen cross-linking treatment. However, it's unclear how long CXL's stiffening impact will last. Over time, another procedure might be required because the expected collagen turnover in the cornea is two to three years. Treatment with cross-linking is not possible if the cornea is less than 400um. Therefore, advanced keratoconus is not a good fit for it. However, in treating progressive keratoconus, the benefits of collagen cross-linking generally exceed the drawbacks [12]. The majority of study data show that corneal stiffness is caused by CXL. It has been observed that the overall stiffness of human corneas can rise by up to 330%. In clinical settings, applation tonometers, such the Goldmann applanation tonometer (GAT), are commonly used to assess intraocular pressure (IOP). Standard corneal stiffness is the foundation for the operation of applanation tonometers [13]. Changes in corneal thickness or curvature can also impact the accuracy of IOP measurements, but changes in corneal rigidity have been demonstrated in a theoretical model to have an even greater impact [14]. The fundamental presumptions of this applanation tonometer might be overstated following CXL, which essentially modifies the corneal biomechanics [15]. Geographical location has a significant impact on the prevalence of keratoconus, which has been found to vary from 0.3 per 100,000 in Russia to 2300 per 100,000 in Central India (0.0003%–2.3%).Places with warmer temperatures and more sunshine, like the Middle East and India, are more common than places with colder temperatures and less sunshine, such Finland, Denmark, Minnesota, Japan, and Russia. The disparities in the reported prevalence

of keratoconus may be explained by ethnic variances. Two surveys conducted in the United Kingdom revealed that Asian respondents (Bangladesh, Pakistan, and India) had a prevalence that was 4.4 and 7.5 times higher than that of white Caucasians. These findings are consistent with the greater prevalence values observed in India [16].

Since Bangladesh is part of the Indian subcontinent, keratoconus is frequent there. To treat keratoconus patients, certain eye care facilities in Bangladesh have started using riboflavin to crosslink corneal collagen in their cornea departments. Among them is our organization. Thus, we have a fantastic chance to further our understanding of CXL in keratoconus. In keratoconus eyes, prior research [2, 4] has demonstrated a marked rise in intraocular pressure both prior to and during corneal collagen crosslinking. This suggests that the primary objective of CXL treatment—a growing corneal resistance—may be accurately and seriously indicated by routine intraocular pressure measurements. This study aims to measure the intraocular pressure in eyes with keratoconus following corneal collagen crosslinking with riboflavin and ultraviolet A, to assess the mean intraocular pressure pre- and post-crosslinking with riboflavin and ultraviolet A at the 1st, 3rd, and 6th month postoperatively in eyes with keratoconus, and to determine the differences in mean intraocular pressure measurements pre- and post-crosslinking with riboflavin and ultraviolet A at the 1st, 3rd, and 6th month postoperatively in eyes with keratoconus.

Material And Methods

It was a prospective observational study and was done in department of cornea, Ispahani Islamia Eye Institute & Hospital. Dhaka. This study was carried out in one year. Permission from ethical committee of Isphani Islamia Eye Institute & Hospital was taken. Patients with keratoconus had corneal collagen crosslinking with riboflavin and ultraviolet A in the cornea clinic of Ispahani Islamia Eye Institute and Hospital. Purposive sampling method was used in the current study.

Patients with keratoconus had corneal collagen crosslinking with riboflavin and ultraviolet A was included. Central corneal thickness <400 microns, pregnancy, severe dry eye syndrome, known case of glaucoma and steroid responder, and any inflammatory process on the ocular surface before CXL procedure were a part of exclusion criteria. Patients with changes in the intraocular pressure after corneal collagen crosslinking with riboflavin and ultraviolet A in eyes with keratoconus were study variables. Sample size has been calculated with the formula:

$n = Z2\ pq / e2$

Here

n = Sample size

Z = 1.96 (Z value of standard normal distribution at 5% level of significance)

p = 2.3% (p =0.023) proportion we except to find keratoconus

q = (1-p) = (1- 0.023) = 0.977

e = 0.05 (Acceptable error in the estimate of p, which is set at 10% of p)

Using above formula the expected sample size:

$n = (1.96)2 \times 0.023 \times 0.977$

$(0.05)2 = 34.52$

Estimated sample size is 34. But due to rarity and limitation of time 30 cases were taken in above mentioned period. All patients with a diagnosis of keratoconus who were have CXL, were willing to comply with the protocol and provided informed written consent, were enrolled in the study. At the time of initial enrollment, all the patients received a complete ophthalmic examination consisting of BCVA, slitlamp biomicroscopy, IOP, CCT and corneal topography. The decision and procedure of CXL was performed by cornea consultant of this institute. After CXL during postoperative follow up visits with the schedule on month 1, 3 and 6 a brief ophthalmological examination done including IOP. Corneal CXL was performed under sterile conditions. The patient's eye was anesthetized with proparacaine hydrochloride 0.5% eyedrops. A 9mm diameter trephine was used to remove corneal epithelium after exposure with 30% alcohol for 30 to 40 seconds. Then riboflavin 0.1% solution was instilled drop by

drop for approximately 10 minutes. Ultraviolet A irradiation was performed using a commercially available UVA system. Irradiance was performed for 5 minutes. At the end of the procedure, a bandage contact lens was applied until full re-epithelialization, typically after 4 days. Tonometry measurements were performed by GAT using a sodium fluorescein at the center of the cornea; the median of 3 consecutive measurements was used for analysis. The aims and objectives of the study along with its procedure, methods, risks and benefits of this study were explained to the patients and their guardians in easily understandable local language and then informed written consent was taken from the patients and legal guardians. It was assured that all information and records kept confident. Data were collected in a pre-designed data collection sheet. All data were analyzed by a statistical software SPSS version 20. A p value of less than 0.05 was considered statistically significant. The results were given as number and percentages for qualitative variables, and mean and standard deviation for quantitative variables.

Results

Thirty one eyes of 30 patients of cornea clinic of Ispahani Islamia Eye Institute and Hospital which fulfill the inclusion and exclusion criteria were enrolled in this study. Age distribution of study subjects shows that out of 30 patients, age of 11 (36.7%) patients were 15 years, 9 (30.0%) were 16-20 years, 9 (30.0%) were 21-25 years and 01 (03.3%) were >25 years. Mean age of the patients was 18.0±4.4 years (range 11-27 years) (Table 1, Figure 1). Table 2 shows that male female ratio was 6.5:1. Gender distribution of the study subjects shows that out of 30 patients, 26 (86.7%) were male and 4 (13.3%) were female (Table 2, Figure 2). Out of 30 patient' laterality of eye involvement, right eyes were in 15 (50.0%), left eyes were in 14 (46.7%) patients and both eyes were involved in 1(3.3%) patients (Table 3, Figure 3). In this study the mean IOP measurement was 10.03±2.09 mmHg (range 6 to 13 mmHg) before CXL, 11.23±1.86 mmHg (range 7 to 14 mmHg) 1 month postoperatively, 12.42±1.86 mmHg (range 8 to 16 mmHg) 3 months postoperatively and 12.94±1.98 mmHg (range 8 to 17 mmHg) at 6 months. The mean intraocular pressure at 1st month, 3rd month and 6th month after CXL were statistically significantly ($p<0.05$) increased compare with before CXL (Table 4, Figure 4).

Table 1. ***Distribution of the study patients by age (n=30)***

Age (in year)	Number of patients	Percentage
15	11	36.7
16-20	9	30.0
21-25	9	30.0
>25	1	3.3
Mean ±SD	18.0	±4.4
Range (min-max)	11	-27

Table 2. ***Distribution of the study patients according to gender (n=30)***

Gender	Number of patients	Percentage
Male	26	86.7
Female	4	13.3

Table 3. ***Distribution of study patients according to side involvement (n=30)***

Side involvement	Number of patients	Percentage
Right	15	50.0
Left	14	46.7
Both (right & left)	1	3.3

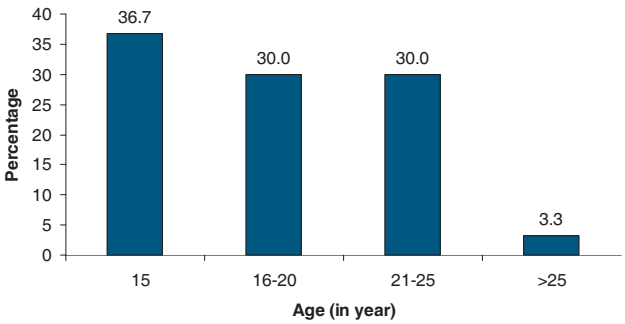

Figure 1: Graphical explanation of age distribution of the study patients.

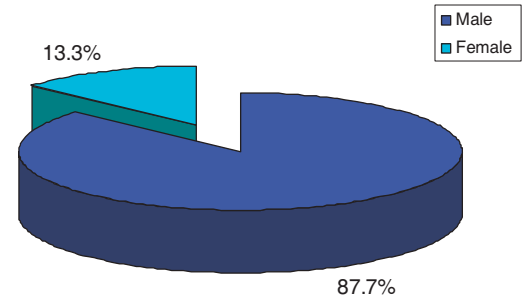

Figure 2: gender distribution of the study patients

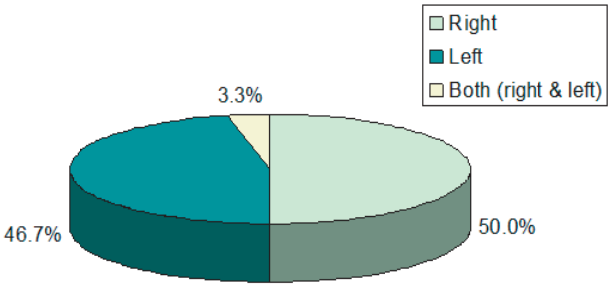

Figure 3: side involvement of the study patients

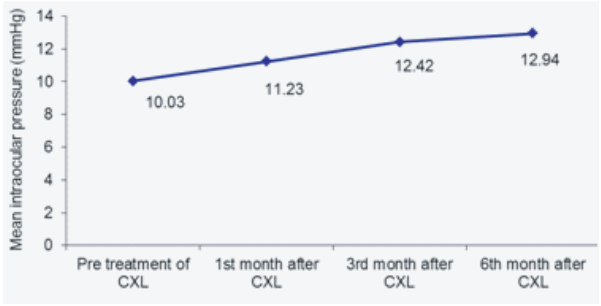

Figure 4: The mean intraocular pressure before and after CXL in different follow up

Table 4. ***Intraocular pressure measurements before and after CXL in different follow up (n=30)***

Intraocular pressure	Eye	Mean±SD	Min-max	P value
Pretreatment of CXL	31	10.03±2.09	6.0-13.0	
1st month after CXL	31	11.23±1.86	7.0-14.0	0.001s
3rd month after CXL	31	12.42±1.86	8.0-16.0	0.001s
6th month after CXL	31	12.94±1.98	8.0-17.0	0.001s

Discussion

Since the 18th century's first description of keratoconus, the ophthalmic community has long been searching for a method to stop the potentially devastating progression of the most common, naturally occurring, non-inflammatory ectatic corneal disorder. The recent introduction of the corneal collagen crosslinking with riboflavin a minimally invasive para-surgical technic that induces a photopolymerization of the altered stromal collagen fibers by the combined action of a photosensitizing substance (riboflavin, vitamin B_2) and ultraviolet A light exposure emitted at 370 nm from a suitable source. It has shown the ability to safely increase of at least three times the rigidity by strengthening the collagen stromal structure thus stabilizing ectatic corneal disorders and inducing a moderate improvement of corneal surface irregularity and visual acuity over time. It's prevalence in studies can range from 0.3 per 100,000 in Russia to 2300 per 100,000 in Central India (0.0003%-2.3%) [3]. As Bangladesh is a country of Indian subcontinent keratoconus is common to our country and now a day's some eye care centers of Bangladesh have well equipped cornea department and they are starting corneal collagen crosslinking with riboflavin to treat keratoconus patients. Our institution one of them. So, we have great opportunity to do more research on CXL in keratoconus. In this present study, the mean age was found 18.0±4.4 years with range from 11 to 27 years and it was observed that more than one third patients were belonged to age 15 years. In a study conducted by Kasumovic et al.[4] they found the average age of the patients was 26.8±1.67 years. Previous studies [17-20] demonstrated that both are the western colder climate countries. Keratoconus in this subcontinent presents at younger age than in western population, with higher prevalence and progresses more rapidly. In our study the mean age of the patients were lower than the above mention studies which coincide with the above statement. In two studies [3, 5] from North India and one from Western India, keratoconus was noted more often in males, while the Central India study found a higher prevalence in women. In this study it was observed that males were predominant (86.7%) than females (13.3%). Male female ratio was 6.5:1. To determine the possible effect of CXL with riboflavin and UVA on IOP measurements was the task of many studies;

results in a recent in vitro study indicate overestimation of true IOP, in the range 1.8 to 3.1 mmHg depending on the tonometer type (GAT, dynamic contour tonometry, Tono-Pen XL).

Nevertheless, this overestimation expected from theoretic calculations, despite a reported increase in corneal rigidity after CXL in human corneas of up to 330%.This result might be because CXL has the maximum stiffening effect in the anterior corneal stroma. In the study, Kasumovic et al. evaluated thirty eyes (30 patients) with central keratoconus. The intraocular pressure was checked by Goldmann applanation tonometry before, 3, 6 and 12 months after CXL. The IOP before the CXL was 12.0mmHg (10.62-15.25 mmHg), 3 months later 13.5mmHg (11.0-16.0mmHg), 6 months 14.0mmHg (11.0-16.0mmHg) and 12 months later 15.0 mmHg (10.37-17.25 mmHg). The value of IOP of 3, 6 and 12 months were statistically significantly higher ($p=0.015$, $p=0.010$) than before CXL. In another study of Kymionis et al. [2] evaluated 55 eyes and found there was a statistically significant increase in the measured IOP 6 months and 12 months after CXL (both $P<.001$) than before CXL. The mean measured IOP was 9.95±3.01 mmHg before CXL, 11.40±2.89mmHg at 6 months and 11.35±3.38mmHg at 12 months after CXL. It was interpreted that after riboflavin–UVA CXL in eyes with keratoconus, there was a significant increase in IOP measured by GAT that was probably caused by an increase in corneal rigidity. In our study it was observed that intraocular pressure at pretreatment of CXL was found 10.03±2.09 mmHg, 1st month after CXL was 11.23±1.86 mmHg, 3rd month after CXL was 12.42±1.86 mmHg and 6th month after CXL was 12.94±1.98 mmHg. Mean intraocular pressure at 1st month after CXL, 3rd month after CXL and 6th month after CXL were statistically significantly increased ($p<0.05$) compare with pretreatment of CXL. This result has good concordance with the findings of other studies. We observe different studies [2-5] including our study shows CXL with riboflavin and ultraviolet A alter the biomechanical properties of keratoconus cornea and increase ocular rigidity, which gives significant overestimation of intraocular pressure measured by Goldmann applanation tonometry. But, we cannot exclude the possibility that the true intraocular pressure may increase after CXL. This possibility could be verified, the corneal collagen crosslinking procedure may have an unknown effect on intraocular pressure. The current study has some limitations e.g., the study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture. Small sample size was also a limitation of the present study. The corneal collagen crosslinking procedure may have had an unknown effect on IOP readings. Another limitation is the IOP measurements were by GAT only, without the use of other tonometer devices.

Conclusion

There was a significant increase in intraocular pressure measured by GAT after riboflavin–UVA CXL in eyes with keratoconus that was probably due to an increase in corneal rigidity. It means the regular measurement of IOP by GAT could be the serious and confident indicator of increasing of corneal resistance which is the main goal of CXL treatment. There are some recommendations from our study like studies should be in multiple centers. In future further study may be under taken with large sample size. IOP should be measured by other tonometer also central corneal thickness take in count.

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