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Posted Date: 2 October 2024

doi: 10.20944/preprints202410.0193.v1

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Efficacy of KeraVio with Irradiation via Violet Light-Emitting Glasses without the Administration of Riboflavin Drops for Progressive Keratoconus Treatment

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ABSTRACT: KeraVio is a new portable corneal cross-linking (CXL) treatment modality in which violet light (VL)-emitting spectacles are used along with topical transepithelial riboflavin. We preliminarily identified endogenous riboflavin in the human cornea without the administration of riboflavin drops, and the relatively low intensity of VL irradiation increased corneal stiffness in porcine corneas (TVST 2021). This study was conducted to evaluate the clinical results of KeraVio without riboflavin drops. Patients with progressive keratoconus were enrolled and randomly divided into the VL irradiation alone group (Group 1) and the no irradiation group (Group 2; control group) (jRCTs032190267). The eyes were exposed to VL (375 nm, irradiance 310 μW/cm2)-emitting glasses for 4.5 hours daily for 6 months. The mean changes in the maximum keratometry value (Kmax) from baseline to 6 months were 0.94 ± 2.65 diopters (D) and 1.76 ± 2.75 D in Group 1 and Group 2, respectively (p=0.705). No differences were found between patients who did and did not receive VL irradiation in terms of the clinical outcomes of keratoconus. VL irradiation alone likely does not halt keratoconic progression, and the administration of riboflavin is necessary.

Keywords: keratoconus; corneal cross-linking; violet light; riboflavin

1. Introduction

Keratoconus is a progressive disorder that involves frequently asymmetric, inflammatory corneal thinning and is characterized by changes in the structure and organization of corneal collagen [1]. This disease induces the progression of corneal thinning, progressive myopia, and irregular astigmatism. Keratoconus has traditionally been treated with corneal transplants to correct vision [2]. Even today, advanced and severe cases of keratoconus still require corneal transplants [3].

Corneal cross-linking (CXL) has been around for over 20 years, with the Dresden protocol being the most popular. The Dresden protocol involves the removal of the corneal epithelium, administration of riboflavin eye drops, and administration of ultraviolet-A (UVA) light. Recently, various techniques have been developed as minimally invasive methods, including the epi-on method, supplemental oxygen administration, pulsed energy therapy, and iontophoresis. A recent review found that around 20 different CXL protocols have been developed [4].

One of these potential therapies for keratoconus that is still under investigation involves the use of violet light (VL)-emitting glasses (Tsubota Laboratory, Inc.) [5]. KeraVio halted disease progression in patients with keratoconus, and its mechanism is similar to that of CXL. KeraVio treatment involves the use of eyeglasses with a 375-nm-wavelength VL source applied to the cornea, and patients wear the eyeglasses daily without limitations. Corneal epithelial peeling in CXL has several potential risks,

 doi:10.20944/preprints202410.0193.v1

including ocular pain and corneal infection after surgery. We are still development of KeraVio treatment, and have confirmed that low-intensity VL irradiation enhanced corneal elastic modulus by focusing on endogenous riboflavin in the human corneal stroma without administering riboflavin eye drops [6]. Our hypothesis is that it would be possible to confirm the effects of KeraVio treatment without administering drugs. Physiological riboflavin in the human corneal stroma itself may affect corneal stiffness by VL irradiation.

This study aimed to report the clinical outcomes of KeraVio with VL irradiation without the administration of riboflavin drops in patients with progressive keratoconus.

2. Methods

We performed a prospective, four-center, randomized controlled study to assess the efficacy outcomes of KeraVio treatment without the administration of riboflavin drops. Institutional review board approval was achieved. The study adhered to the tenets of the Declaration of Helsinki. The study participants addressed a written informed consent form. This study was approved by the Review Board at Shinanosaka Clinic and registered in the Japan Registry of Clinical Trials (jRCT): jRCTs032190267.

2.1. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: male or female sex; any race or ethnicity; an age of 7 years or older; and a diagnosis of keratoconus as documented by topography or tomography. Subjects were also required to have exhibited progression within 6 months before baseline to receive KeraVio treatment, as defined by one or more of the following: (1) an increase of ≥0.50 diopters (D) in the maximum keratometry value (Kmax); (2) an increase of ≥0.50 D in cylinder power on subjective manifest refraction; (3) an increase of ≥0.50 D in myopia on subjective manifest refraction; and (4) a decrease of ≥5 μm in the thinnest corneal thickness. Contact lenses were removed for a period before each visit to avoid the changes in corneal shape. The period was 3 weeks for rigid gas-permeable lenses and 1 week for soft contact lenes. The combination with the use of contact lenses and KeraVio treatment was limited to VL-transmitting lenses [7].

The exclusion criterion included a history of corneal surgery, including intracorneal ring segment surgery. Subjects who may become candidates for corneal transplantation during the observation period were excluded.

2.2. KeraVio Treatment

The subjects were randomly and equally assigned to the KeraVio with VL irradiation group and control group, so that the ratio of the trial to control patients was 2:1. In the KeraVio with VL irradiation group, the subjects wore VL-emitting glasses [5], and their corneas were aligned and exposed to VL (375 nm) for 4.5 hours daily for 6 months. Before each treatment, the desired irradiance of 0.31 mW/cm2 was verified with a UVA meter (LaserMate-Q; LASER 2000, Wessling, Germany) at a distance of 1.2 cm from the cornea and, if necessary, regulated with a potentiometer. With respect to the control group, the participants could have readily noticed if the eyeglasses emitted no light. Therefore, although the frames were identical in both groups, we made pseudo-placebo glasses for the control group with a minimal amount of VL irradiance (<0.01 mW/cm2) to maintain the double-blind nature of the study. The participants were masked by removing all eyeglass labels before they received the glasses [8]. The total energy doses of VL using eyeglasses for 6 months in the KeraVio with VL irradiation group and the control group were 904.0 and 29.2 J/cm2, respectively.

If both eyes per subject met the inclusion criteria, only the more severely affected eye was selected for treatment, after which a randomization procedure was performed for the two groups. The eye that was not treated was not exposed to VL by shielding the LED light source in the glasses.

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2.3. Outcome Measures

Tomography. Tomographic data were obtained via anterior segment optical coherence tomography (AS-OCT) (CASIA™, Tomey Corporation, Nagoya, Japan) at baseline and at 1, 3, and 6 months after KeraVio treatment. For quantification of keratometric parameters, the minimum corneal thickness and stromal demarcation line (DL) identified by the AS-OCT system were analyzed. Kmax was chosen as the primary efficacy outcome because it measures a salient feature of corneal ectasia, that is, the steepness of ectatic tomographic distortion. The identification of the DL via the AS-OCT scan was evaluated by two independent observers 1 month after treatment, as analytically determined in our previous studies [9,10].

Visual Acuity and Refraction. The uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and manifest refraction spherical equivalent (MRSE) were measured at baseline and at 1, 3, and 6 months after KeraVio treatment. Visual acuity measurements were obtained as the logarithm of the minimal angle of resolution (logMAR) units via a Landolt C chart.

In terms of the safety indices of VL in eyes, these indices were verified in our previous clinical trial, and we did not include these items from the present study.

2.4. Statistical Analysis

All statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA). Sample size calculation was performed using PASS 2008 software (NCSS, Kaysville, Utah, USA). The outcome measures are reported as the mean ± standard deviation. Normality of all data samples was first checked by the Kolmogorov-Smirnov test. The Mann–Whitney U test was used to compare the data between the two groups. A P value of < 0.05 was considered statistically significant. The sample size (n=18:8, in each group) in this study offered 92% statistical power at the 5% level to detect a 0.6-D difference in Kmax between the two groups when the standard deviation of the mean difference was 0.4 D.

3. Results

3.1. Subject demographics

Eighteen eyes belonging to 18 patients were treated with KeraVio without the administration of riboflavin drops. Additionally, eight eyes of 8 patients were included in this study as a control group. The participant demographics are presented in **Table 1**. At baseline, the age and Kmax values in the KeraVio with VL irradiation group did not differ from those in the control group ($P = 0.219$ and $P = 0.816$, respectively). All patients remained in the study through the 6-month follow-up.

Table 1. Demographics of patients in the KeraVio with violet light irradiation group.

	KeraVio with VL irradiation	Control	*P value
Eyes/patients (n)	18/18	8/8	n/a
Age (yrs)	28.56 ± 11.96	40.25 ± 11.72	0.219
Sex (female/male) (n)	14/4	6/2	n/a
Kmax (diopters)	56.17 ± 9.18	56.18 ± 8.35	0.816

*Compared with the control group. n/a = not applicable.

3.2. Corneal Parameters

Table 2 shows the changes in Kmax and thinnest corneal thickness values from baseline to the 6-month observation period after treatment. No significant differences were detected in the Kmax or thinnest corneal thickness between the two groups during the 6-month observation period. The mean changes in Kmax from baseline to 6 months in the KeraVio treatment with VL irradiation and control groups were 0.94 ± 2.65 D and 1.76 ± 2.75 D, respectively ($P = 0.705$). Similarly, the mean changes in the thinnest corneal thicknesses were -6.44 ± 19.16 μm and -0.50 ± 2.95 μm, respectively ($P = 0.029$).

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The corneal stromal DL was identified in only one eye (5.6%) by both examiners in the KeraVio with VL irradiation group at 1 month. No DL was found in the control group.

Table 2. Changes in corneal parameters over time.

	Baseline	1 month	3 months	6 months	Change from baseline to 6 months
Kmax (D)					
KeraVio with VL irradiation	56.17 ± 9.18	55.75 ± 8.93	55.88 ± 9.43	57.11 ± 10.17	0.94 ± 2.65
Control	56.18 ± 8.35	56.43 ± 10.04	57.29 ± 10.18	57.23 ± 7.85	1.76 ± 2.75
*P value	0.816	0.816	0.600	0.624	0.705
Thinnest corneal thickness (μm)					
KeraVio with VL irradiation	429.47 ± 63.54	428.88 ± 64.45	424.24 ± 64.84	422.24 ± 67.85	-6.44 ± 19.16
Control	415.63 ± 77.14	408.63 ± 80.66	417.63 ± 80.57	417.17 ± 79.10	-0.50 ± 2.95
*P value	0.600	0.462	0.641	0.753	0.029

*Compared with the control group. D=diopters

3.3. Visual Acuity and Refraction

Table 3 shows the changes in CDVA, UDVA, and MESE from baseline to the 6-month observation period after treatment. No significant differences between the two groups were detected in these parameters during the 6-month observation period. The mean changes in CDVA from baseline to 6 months in the KeraVio with VL irradiation and control groups were 0.03 ± 0.13 logMAR and 0.04 ± 0.12 logMAR, respectively (P = 0.616). Similarly, the mean changes in UDVA were -0.09 ± 0.42 logMAR and 0.02 ± 0.30 logMAR, respectively (P = 0.404).

The mean changes in MRSE from baseline to 6 months in the KeraVio with VL irradiation and control groups were 0.91 ± 2.40 D and 0.03 ± 0.53 D, respectively (P = 0.304).

Table 3. Changes in visual acuity and refraction over time.

	Baseline	1 month	3 months	6 months	Change from baseline to 6 months
Corrected distance visual acuity (logMAR)					
KeraVio with VL irradiation	0.20 ± 0.42	0.25 ± 0.48	0.27 ± 0.50	0.24 ± 0.46	0.03 ± 0.13
Control	0.33 ± 0.41	0.31 ± 0.39	0.39 ± 0.46	0.37 ± 0.49	0.04 ± 0.12
*P value	0.534	0.728	0.388	0.604	0.616
Uncorrected distance visual acuity (logMAR)					
KeraVio with VL irradiation	0.84 ± 0.59	0.82 ± 0.63	0.80 ± 0.69	0.74 ± 0.61	-0.09 ± 0.42
Control	0.98 ± 0.47	0.87 ± 0.73	0.90 ± 0.72	1.07 ±0.80	0.02 ± 0.30
*P value	0.600	0.863	0.918	0.352	0.404
Manifest refraction spherical equivalent (D)					
KeraVio with VL irradiation	-6.57 ± 7.29	-6.54 ± 7.21	-6.15 ± 6.89	-5.67 ± 7.50	0.91 ± 2.40
Control	-7.73 ± 7.42	-7.67 ± 7.30	-7.97 ± 6.83	-7.04 ± 7.70	0.03 ± 0.53
*P value	0.999	0.864	0.682	0.680	0.304

*Compared with the control group. logMAR=logarithm of the minimal angle of resolution. D=diopters

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4. Discussion

In the present study, no significant differences in Kmax, vision, or refraction were observed between the group that received KeraVio treatment with VL irradiation without the administration of riboflavin drops and the control group during the 6-month observation period. Therefore, no differences were found between patients who did and did not receive VL irradiation in terms of the clinical outcomes of keratoconus. VL irradiation alone likely does not halt keratoconic progression, and the administration of riboflavin might be necessary to achieve significant efficacy in KeraVio treatment. The change in thinnest corneal thicknesses was thinner in the VL group compared with the control group, but the interpretation of this result is difficult. It may be within the margin of error or the reliability of the its measurement may not be valid. We focused on the results of Kmax, vision, and refraction. On the other hand, in ex vivo porcine corneas, the KeraVio without riboflavin (VL irradiation only) and standard CXL groups presented significantly greater elastic moduli than the normal control group did, whereas no significant difference between the VL-only group and the CXL group was found [11]. These findings suggest that treatment involving only VL irradiation to the cornea is insufficient to inhibit the progression of keratoconus and that the administration of riboflavin eye drops might be needed to ensure the efficacy of KeraVio.

To confirm the effectiveness of KeraVio and CXL for keratoconus, it is important to confirm the presence or absence of the DL. In the present study of KeraVio treatment with VL irradiation alone, the DL was confirmed in only one eye of 18 patients (5.6%). On the other hand, in our previous clinical trial in which 0.05% flavin adenine dinucleotide (FAD) (Santen Pharmaceutical Co., Ltd., Osaka, Japan) eye drops were used in combination with KeraVio treatment, the DL was observed in 16 eyes of 20 patients (80%) [5]. FAD plays a role as a coenzyme of riboflavin [12,13]. The mean Kmax value of the KeraVio-treated eyes decreased by 0.81 D at 6 months, suggesting that FAD or riboflavin eye drops are essential for the cessation of keratoconus progression [5]. In Japan, FAD eye drops have long been used to treat keratitis, but owing to the influence of pharmaceutical regulations, the distribution of the active pharmaceutical ingredient was suspended in 2022. We are still looking for ways to provide KeraVio treatment without FAD eye drops, but it was confirmed that the combination of VL irradiation and FAD eye drops is a prerequisite for efficacy in this clinical trial. We plan to create a new system to supply FAD eye drops or develop a protocol for oral riboflavin supplementation.

As a limitation of the present study, the sample size was not large; this was a pilot study conducted to evaluate the efficacy of KeraVio treatment with VL irradiation and without the administration of FAD drops. Considering the minimization of risk and the sufficient sample size, the sample size of this study was set at 26 patients in total.

In conclusion, based on our 6-month follow-up results, no differences were found between patients who did and did not receive VL irradiation in terms of the clinical outcomes of keratoconus. VL irradiation alone likely does not halt keratoconic progression, and the administration of riboflavin is necessary.

Meeting Presentation: This study was presented as a free paper at the 1st World Keratoconus Congress.

Running head: KeraVio without Riboflavin Drops

Contributors: Conception and design: Kobashi, Tsubota Analysis and interpretation: Kobashi, Kumanomido, Ide, Kato, Shimazaki, Itoi Data collection: Kobashi, Kumanomido, Ide, Kato, Shimazaki, Itoi**;** Obtained funding: Kobashi, Tsubota**;** Overall responsibility: Kobashi, Tsubota

Funding: This work was supported by Tsubota Laboratory Inc.

Disclaimer: The sponsor had no role in the study design; data collection, analysis or interpretation; writing of the report; or the decision to submit the article for publication.

Competing interests: The author(s) disclose the following: H.K.: Consultant and equity owner, Tsubota Laboratory Inc. (Tokyo, Japan); Patent, Tsubota Laboratory Inc. K.T.: Employee and equity owner, Tsubota Laboratory, Inc.; Patent, Tsubota Laboratory, Inc. No other disclosures were reported.

Patient consent for publication: Not required.

 doi:10.20944/preprints202410.0193.v1

Ethics approval: The study adhered to the tenets of the Declaration of Helsinki. The study subjects completed a written informed consent form. This trial was approved by the Certified Review Board of Shinanosaka Clinic and registered in the Japan Registry of Clinical Trials (jRCT): jRCTs032190267.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: Data are available upon reasonable request.

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