

In-vivo Corneal Temperature during Cross-linking Measured by an Infrared Thermometer

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Abstract

Introduction: The crosslinking technique (CXL) is proposed to the patient to increase rigidity of the cornea in case of evolutive keratoconus. It is based on a photopolymerization of collagen fibers by the action of ultraviolet radiation. This technique requires energy supply which can be done in the form of heat, or irradiation by particles (e.g. electrons or photons) for a long time. It would be therefore legitimate to have data regarding the in-vivo temperature of this cornea irradiated by UV-A through a precise, reproducible and non-invasive method.

Patients and methods: In this prospective study since February 2017 to November 2017, it is proposed to measure the corneal temperature with a non-contact infrared thermometer (Benetech gm 320)* in °C on the center of the cornea. A first study involved 48 normal volunteers, of different age and sex, afebrile, possessing all a pachymetry between 520 and 550 μ , in order to have the average corneal temperature which will serve us as a reference for our study. The temperature will then concern 46 patients, afebrile, presenting a keratoconus with an average pachymetry of 460 μ (\pm 52 μ), benefiting in our service of sessions of CXL epi-on with the standard protocol (energy: 3 Mw, duration: 30 min) and with the same room temperature in the room. The average age of patients at time of the procedure was 19.6 (\pm 3.7) years. The temperature is taken at a fixed distance (11 cm) every 5 min from the moment of application of Riboflavin (0.25% Riboflavin, 1.2% HPMC, 0.01% Benzalkonium Chloride) on the cornea until the end of the CXL session.

Results: The corneal temperature of the whole control group was 33.97 ± 0.20 . The corneal temperature curve showed a very slight increase during the application of Riboflavin alone ($+0.21^{\circ}\text{C}$) but when exposed to UV-A, temperature increased on average by $+1.1^{\circ}\text{C}$ with maximum temperatures not exceeding 35.5°C .

Discussion: The exposure of the cornea to irradiation by UV-A, not only by patients but also by some ophthalmologists, increases the corneal temperature which is limited to 1°C .

Conclusion: Looking forward to a broader study with different crosslinking strategies, this study has the merit of introducing this tool of non-invasive and accurate measurement of corneal temperature in-vivo. The data in this study show increase in corneal temperature by an average of 1°C during crosslinking sessions spike with the standard strategy.

Keywords: Cornea; Crosslinking; Temperature; Infrared thermometer; Corneal surface; Keratoconus; Riboflavin; UV-A

Introduction

The CXL technique was discovered by Dr. Théo Sellar's team at the University of Dresden in the late 1990s while studies in humans began in 2003 [1]. The goal of this treatment is to stop progressive and irregular changes in the shape of the cornea known as ectasia. These ectatic changes are typically marked by corneal thinning and increased anterior and/or posterior curvature of the cornea, and often lead to high levels of myopia and astigmatism. The most common form of ectasia is keratoconus [1-5].

This technique requires the addition of a molecule of riboflavin (also called vitamin B2) and the irradiation of corneal tissue with ultraviolet A (UVA) photons. Riboflavin must impregnate the corneal stroma [6-9]. Irradiated by UVA (particularly energetic radiations), this molecule generates free radicals containing oxygen, which would be at

the origin of the creation of covalent bonds [1,2,10,11]. Crosslinking of corneal collagen is therefore intended to "stiffen" a biomechanically unstable cornea [10,11]. The principle is based on a photo-induced biochemical "bridging" of collagen fibers [1,2,5,7].

The main goal of the first stage of therapy is to allow riboflavin to diffuse into the cornea. The techniques used to accomplish this all involve either eliminating or weakening the epithelial barrier of the cornea. Conventionally, cross-linking requires central de-epithelialization in an operating room with strict sterilization conditions. It is a source of postoperative pain and sometimes of infection [12-16].

The objective of the CXL epi-on is therefore the treatment of keratoconus without pain and without complications related to the de-epithelialization: infections, infiltrates, corneal edema, delayed healing, etc. [17-20]. The addition of passage-facilitating molecules, such as EDTA or BAC, or a combination of both, breaks the intercellular junctions to allow riboflavin to pass into the stroma [4-7]. This

transepithelial technique is the one used in our ophthalmology department B, at RABAT CHU.

Regarding ultraviolet radiation, it is an invisible radiation that emits in the wavelength range of 100 to 400 nm. It has a shorter wavelength than visible light and therefore contains more energy [8,9]. UV radiation is known to be harmful to the endothelium, lens and retina.

Regarding UVA during Cross-Linking sessions [1,2,4,6]:

- The surface irradiance clinically used is 3 mW/cm².
- The wavelength used is 365 nm with a cumulative illumination of 5.4 J/cm².
- The duration is 30 min.

Many patients express their concern about the exposure of their cornea to such exposure to UVA radiation and also some ophthalmologists have questions about the safety of their patients. It is true that the appearance of the cornea during the procedure is quite spectacular and fears a burn of the cornea (Figure 1).

It is therefore legitimate to ask: what is the temperature of the cornea during this exposure to UVA? And that's the purpose of this study.

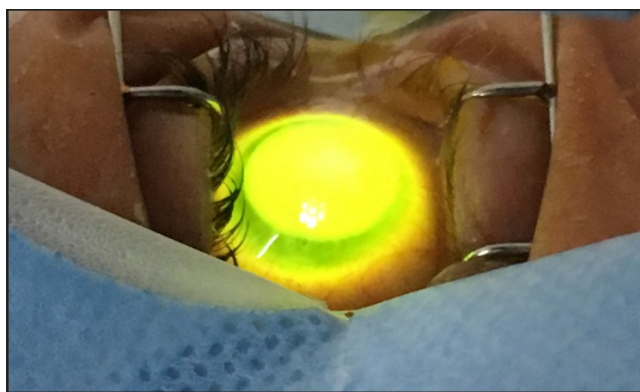


Figure 1: Aspect of the eye during exposure to UVA radiation in corneal cross-linking.

Methods

In this prospective study was carried out at the ophthalmology department B at Rabat University Hospital from February 2017 to November 2017. It was proposed to measure corneal temperature using a non-contact infrared thermometer (Benetech gm320)* during crosslinking sessions in patients with evolutive keratoconus. Exclusion criteria were: patients with fever and pachymetry less than 400 μ m. This study and data collection complied with all national laws and informed consent was obtained from patients (or their parents for minors) and the study was in accordance with the principles of the Helsinki Declaration.

To know the temperature of an object, the thermometer is pointed towards it and the trigger is pressed. The LCD screen with backlighting allows us to get data even in the dark, as is in case of crosslinking room conditions. It has a laser pointer that was not used in our study. Its measurement range is -50 to +380°C. The distance does not interfere with the temperature. Changing the distance only changes the

diameter of the measured surface. The temperature of the room was set at 22°C.

The device was calibrated several times with the mercury thermometer while measuring body temperature, and also with a professional thermometer, the UT151E Modern Digital Multimeters* (figure 2). LIGHTLINK CXL UV-A device was used for this study.

A first study concerned 48 normal volunteers (96 eyes), of different age (between 12 And 70 years) and gender (27 females and 21 males), afebrile, all possessing a pachymetry between 520 and 550 μ m, in order to have the average corneal temperature which served as a reference for our study. The average temperature between the two eyes was recorded for each volunteer. The measurement of the temperature then concern 46 eyes of 46 patients, afebrile, presenting a evolutive keratoconus with an average pachymetry of 453 μ m, benefiting in our service of CXL sessions epi-on with the standard protocol (energy: 3 Mw, duration: 30 min). The average age of patients at the time of the procedure was 19.4 years. The temperature was taken at a fixed distance every 5 min from the time of application of riboflavin on the cornea until 30 min after the end of the CXL session.

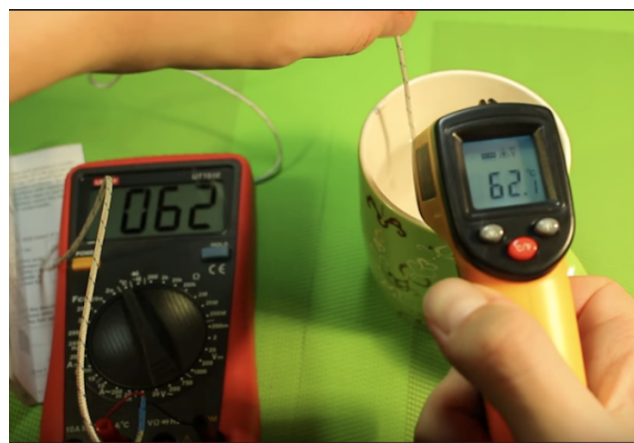


Figure 2: Calibration of the infra-red thermometer.

A Pearson correlation analysis was done to establish the relationship between two continuous variables, such as corneal temperature and age or pachymetry. The coefficient (r) thus refers to the Pearson correlation coefficient in this article. For all analyzes, the level of significance was set at $p < 0.05$. The analysis was conducted using commercially available software (STATA).

Results

Mean corneal temperature for the whole control group was $34.1 \pm 0.6^\circ\text{C}$ (N =48). There was no statistically significant correlation between age and corneal temperature ($r = -0.17$; N=48; $P = 0.248017$). The result is not significant at $p < 0.05$ (Figure 3).

There was no relationship between pachymetry and the temperature of the cornea (N=46; $r = -0.09$; $P = 0.551964$). The result is not significant at $p < 0.05$ (Figure 4).

The group of the 48 patients with keratoconus is elaborated with the different parameters: body temperature, age, gender, temperature before the T0 procedure is indicated, then every 5 min during riboflavin drops T1 to T6, and every 5 min also during the irradiation

UVA, from T7 to T12. The temperature is taken at 15 min and 30 min after the procedure. The measured pachymetry is also indicated.

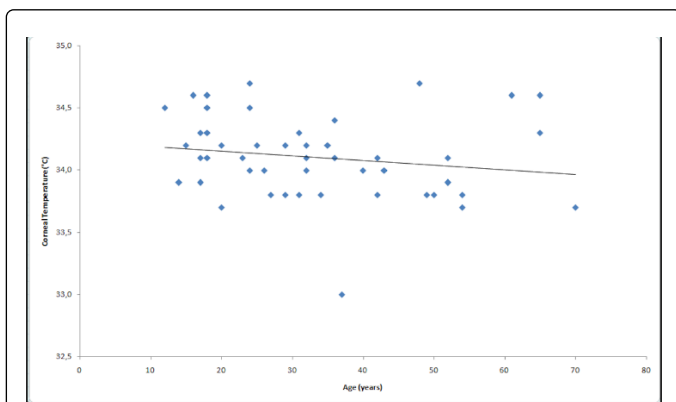


Figure 3: Correlation between age in years and corneal temperature in °C in the control group of healthy subjects. There is no statistically significant correlation between age and corneal temperature.

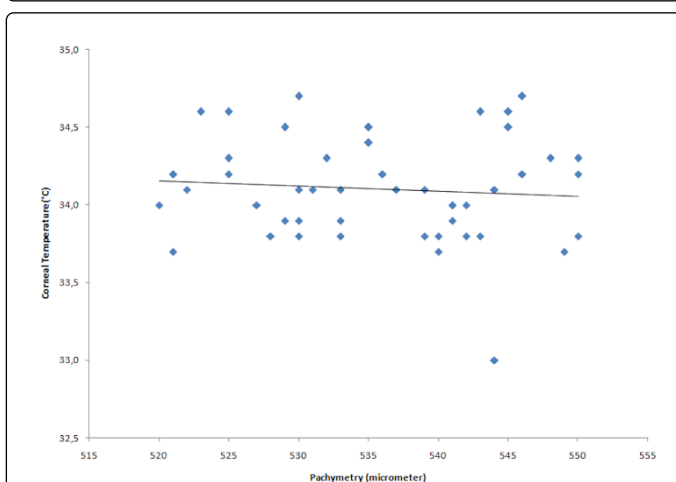


Figure 4: Correlation between pachymetry and corneal temperature in °C in the control group. There is no significant correlation between pachymetry and the temperature of the cornea.

The average temperatures of the whole group were measured every 5 min (Figure 5).

During the riboflavin administration phase, there is little or no increase in temperature. On the other hand, during the UV exposure phase, the temperature of the cornea is increased by an average of 1°C.

So, according to this study (Figure 6):

- The corneal temperature curves showed a very slight increase when applying Riboflavin alone (+0.2°C).
- But when exposed to UV-A the temperature increased on average by +1.1°C.
- The temperature returns to the initial values 30 min after the end of UVA irradiation.

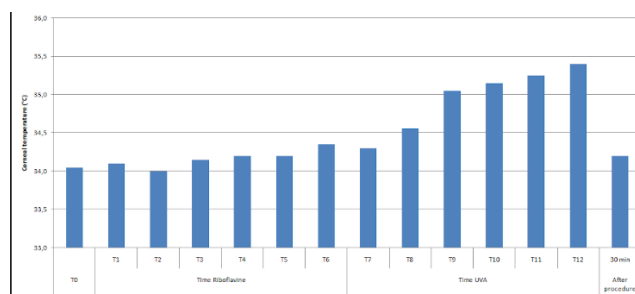


Figure 5: Profile changes in corneal temperature during T0 crosslinking procedure (before application of Riboflavin) then every 5 min during instillation of riboflavin (T1 to T6) and every 5 min during UV-A exposure (from T7 to T12). The temperature is taken also, at 30 min after the procedure.

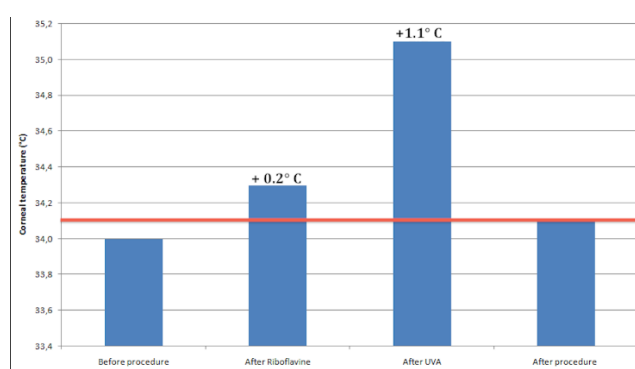


Figure 6: Evolution of the corneal temperature during the crosslinking session from T0 (before the start of the procedure), at T6 (at the end of the instillation of riboflavin), at T12 (at the end of the UV-A exposure), finally, at 30 min after the radiation. The red line indicates the average temperature of the control group.

Discussion

Studies that also measured infrared temperature of the cornea used an infrared camera [21-25]. It gives color ranges by temperature while the device used in our study targets a well-defined area and displays a very accurate result. Apart from precision, the price difference is also huge (the device used in our study cost only 35 USD, while the entry-level infrared camera starts at 3000 USD).

The wavelength of UVA used during crosslinking is between 360-370 nm. The energy in joules of the UVA radiation can be calculated from the following relationship: the wavelength in nanometer=celerity of the light (in km/s) divided by the frequency in THerz. The wavelength is 365 nm and the celerity of the light is 3,00,000 km per second. So we can find the frequency. To calculate the energy in joule:

$$E \text{ (in joules)} = h \text{ (Plank constant)} \times \text{frequency.}$$

With a wavelength of 370 nm and an irradiance of 3 mW/cm² for a total duration 30 min, this corresponds to a total dose density of 5.4 J/cm² [26].

1 joule is the energy needed to raise the temperature of one liter of dry air by 1°C.

The wavelength of the UV light used at 370 nm is not chosen at random: it is a wavelength which corresponds to the maximum absorption of riboflavin. Riboflavin (vitamin B2) is not just a photosensitizer, it also acts as a UV absorber. Because of the extra shielding of riboflavin, all the structures located behind the corneal stroma, including the corneal endothelium, the anterior chamber, the iris, lens and retina are theoretically exposed to a residual density less than 1 J/cm² [20]. Moreover, no retinal or crystalline involvement after CXL has been described in the literature [20].

This study reinforces the veracity of the safety of the procedure, because the increase in the temperature of the cornea after exposure to UVA crosslinking for 30 min, remains about 1°C. This increase in temperature is identical to that which occurs physiologically when closing the eyelids for 5 min [27,28].

Conclusion

Although this study is limited by the small number of patients studied and is performed only on cases of crosslinking epi-on, it is clear that there is an increase in corneal temperature of about 1°C during the crosslinking sessions with the standard strategy.

So contrary to popular belief about exposure of the cornea to irradiation by UV-A, not only by patients, but also by some ophthalmologists, there is increase in corneal temperature which remains limited to 1 degree Celsius.

In anticipation of a broader study with different crosslinking strategies, this study has the merit of introducing this very cheap, non-invasive and accurate tool for measuring corneal temperature *in-vivo*.

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