Effect of Corneal Collagen Cross-Linking on Quality of Life in Patients with Bullous Keratopathy

Kornea Çapraz Bağlama Tedavisinin Büllöz Keratopatili Hastalarda Yaşam Kalitesi Üzerine Etkisi

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ABSTRACT Objective: To evaluate the effect of corneal cross-linking (CXL) on quality of life in patients with bullous keratopathy. **Material and Methods:** The study was designed as prospective, comparative, single-center and nonrandomized cohort. Ten patients with painful bullous keratopathy to whom CXL was applied were included in the study group. Ten consecutive patients with painful bullous keratopathy who didn't accept CXL were admitted as the control group. Besides routine ophthalmic examinations, SF-36 (Short Form-36) questionnaire was also performed to all patients at baseline. All examinations were repeated at first, 3rd, 6th and 12th months. **Results:** A significant improvement in "Physical Functioning" and "Vitality" subscales starting from the first month after CXL, continuing up to the postoperative 6th month (p=0.04, p=0.01, respectively) was achieved. An improvement in "Bodily Pain" subscale was achieved starting at the 3rd month after CXL, and continued until the 6th month (p=0.01, p=0.01, respectively). Unfortunately, there was a deterioration in "Physical Functioning", "Bodily Pain", and "Vitality" subscales starting from the 6th month, with statistically significant variations between the 6th and the 12th months (p=0.02, p=0.02, p=0.02, respectively). In the control group, there was a significant deterioration in "Physical Functioning", "Bodily Pain", "General Health", and "Social Functioning" subscales between baseline and the 12th month (p=0.02, p=0.04, p=0.02, p=0.03, respectively). **Conclusion:** CXL may be useful in the treatment of bullous keratopathy when waiting for keratoplasty, particularly in patients with intense pain by temporarily improving the quality of life.

Key Words: Corneal edema; pain measurement; blister

ÖZET Amaç: Kornea kollajen çapraz bağlama (CXL) tedavisinin büllöz keratopatili hastaların yaşam kalitesi üzerine olan etkisini değerlendirmek. **Gereç ve Yöntemler:** Çalışma prospektif, kontrollü, tek-merkezli ve nonrandomize kohort çalışması şeklinde dizayn edilmiştir. Ağrılı büllöz keratopatili olup CXL tedavisi uygulanan 10 hasta çalışma grubuna dahil edildi. Müteakip tedaviyi kabul etmeyen ardışık 10 hasta kontrol grubu olarak alındı. Başlangıçta tüm hastalara rutin oftalmolojik muayenelerin yanısıra SF-36 (Kısa Form-36) anketi uygulandı. Bütün muayeneler 1., 3., 6. ve 12. aylarda tekrarlandı. **Bulgular:** "Fiziksel işlevsellik" ve "enerji" alt skalalarında CXL sonrası 1. aydan başlayıp 6. aya kadar devam eden anlamlı iyileşme izlendi (sırası ile, p=0,04, p=0,01). "Ağrı" alt skalasında 3. aydan başlayıp 6. aya kadar devam eden iyileşme saptandı (sırası ile, p=0,01, p=0,01). Maalesef, "Fiziksel işlevsellik", "ağrı" ve "enerji" alt skalalarında 6. aydan sonra kötüleşme mevcuttu ve operasyon sonrası 1. yıl ile 6. ay kıyaslandığında bu kötüleşmenin istatistiksel açıdan anlamlı olduğu bulundu (sırası ile, p=0,02, p=0,02, p=0,02). Kontrol grubunda "fiziksel işlevsellik", "ağrı", "genel sağlık algısı" ve "sosyal işlevsellik" alt skalalarında 12. ayda operasyon öncesi döneme göre anlamlı kötüleşme izlendi (sırası ile, p=0,02, p=0,04, p=0,02, p=0,03). **Sonuç:** CXL, büllöz keratopatinin tedavisinde keratoplasti için beklerken özellikle şiddetli ağrısı olan hastalarda yaşam kalitesini geçici süre arttırarak faydalı olabilir.

Anahtar Kelimeler: Kornea ödemi; ağri ölçümü; blister

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Corneal cross-linking (CXL) is an innovative approach to increase the mechanical and biochemical stabilities of the corneal stroma to halt keratoconus progression.[1-3] Although, the genesis aim of CXL procedure was the treatment of keratoconus, a role for CXL has also been suggested as a promising alternative method in managing bullous keratopathy by reducing ocular discomfort, increasing visual acuity and probably postponing or even eliminating the need for corneal transplantation.[4-7]

In the present study we evaluated the effects of UVA CXL following intrastromal 0.1% riboflavin administration on quality of life in patients with bullous keratopathy.

MATERIAL AND METHODS

This prospective, comparative, single-center, nonrandomized cohort study was conducted between June 2011 and February 2013 in accord with the principles of the Declaration of Helsinki, after Ege University Ethical Committee approval. Written informed consent was obtained from all patients included in the study. Ten patients with unilateral painful bullous keratopathy waiting for corneal transplantion were included in the study group. Ten consecutive patients with painful bullous keratopathy who didn't accept CXL treatment, were admitted as the control group. Patients with active corneal infection, history of herpetic keratitis or chemical injury, pregnancy, autoimmune or connective tissue diseases were excluded.

Besides routine examinations (best corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement) SF-36 questionnaire was also performed to all patients at baseline. All examinations and the SF-36 questionnaire were repeated at 1, 3, 6 and 12 months after baseline for the control group and after CXL treatment for the study group. BCVA was measured on a decimal scale and converted to the logarithmic scale [logarithm of the minimum angle of resolution (logMAR)].

Each CXL procedure was performed by the same operator (EK), according to the same protocol. The patients were treated in an operating room under topical anesthesia. Mean operation time was defined as one hour. Eye drop instillation preceding treatment consisted of one drop 0.5% proparakain HCl (Alcaine®, Alcon, Fort Worth, Texas, USA), beginning 5 minutes before the procedure. After applying Betadine antiseptic solution and setting the sterile field with a blepharostat, the central corneal epithelium was mechanically debrided with a 15 blade, over a 9-mm diameter. The cornea was impregnated with a photosensitizing solution of riboflavin 0.1% with 20% dextran T500 (Ricrolin®, SOOFT, Montegiorgio, Italy) by corneal instillation at a rate of one drop in every 2 minutes for 20 minutes. After verification of the UVA laser source unit's calibration using a UVA power meter, the corneal collagen was polymerized for 30 minutes (Vega CBM X-Linker, CSO, Italy LED-UVA single 370-nm beam, 3 $mW/cm^2 \pm 10\%$, 5.4 J/cm^2). The UV beam's focus was checked initially with an aiming beam produced by 2 centering LED (644 nm), and the irradiation was stopped automatically in every 5 minutes for checking the correct focalization of the UV beam. During this second step, riboflavin was instilled regularly to maintain its stromal concentration. After abundant rinsing with balanced salt solution and instillation of one drop of tobramycin (Tobrex®, Alcon, Fort Worth, Texas, USA), a soft bandage contact lens was placed. Postoperative treatment included topical tobramycin four times daily until closure of the epithelial defect, and topical artificial tears (Refresh Tears®, Allergan, Irvine, CA) for at least 1 month. All patients were seen again on the first and the 7^{th} postoperative days, to assess epithelial healing and the absence of infectious complications and to remove the bandage contact lens.

Statistical analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, Illinois). Normal distribution assumption couldn't be accepted for some parameters according to the Shapiro Wilks W-test. Therefore, non-parametric tests were used. Evaluation of intragroup inter temporal changes were evaluated by the Friedman test. When statistically significant results were obtained by the Friedman

test, Wilcoxon test was used for dual comparison. Intergroup comparisons were conducted by U-Test (Mann–Whitney) and Chi-Square test. Results were presented as mean±standard deviation (SD), median, minimum-maximum values. In all analyses, $p<0.05$ was considered statistically significant. This study was performed in accordance with the principles of the Declaration of Helsinki, after Ege University Ethical Committee approval. Written informed consent was obtained from all patients participating the study.

RESULTS

Mean age of the study and the control groups were 61.5±18.2 (range, 30-79) and 60.4±17.7 (range, 30-80) years, respectively (p=0.9). Male to female preponderance in the study and the control groups were 7:3 and 6:4, respectively (p=1.00). Mean preoperative BCVA in the study and the control groups were 2.29±0.9 (range, 0.52-3.10) and 2.27±0.9 (range, 0.80-3.10) logMar, respectively (p=0.9). Mean preoperative IOP in the study and the control groups were 18.3±6.6 (range, 12-30) and 14±1.4 (range, 12-16) mmHg, respectively (p=0.1). In the study group, 5 patients had pseudophakic bullous keratopathy, 3 glaucomatous bullous keratopathy and 2 aphakic bullous keratopathy, while the control group consisted of 7 pseudophakic bullous keratopathy, 2 glaucomatous bullous keratopathy and 1 aphakic bullous keratopathy. No statistically significant variation in BCVA and IOP between pre- and postoperative 12 months were detected in the study group (respectively; p=0.6, p=0.06). No complications due to CXL occurred in the study group.

When scores of SF-36 questionnaire were evaluated for the study group a significant improvement in "Physical Functioning" and "Vitality" subscales starting from the first month after CXL treatment (p=0.04) continuing up to the 6th month of the therapy (p=0.01) was observed (Table 1). An improvement in "Bodily Pain" subscale was achieved starting at the 3rd month after CXL, and continued until the 6th month (p=0.01, p=0.01, respectively), however this improvement did not carry on until the 12th month (p=0.02). Improvements in "General Health" and "Social Functioning" subscales at the 6th month (p=0.04, p=0.01, respectively), and "Mental Health" at the 3rd month (p=0.01) were obtained. Unfortunately, there was a deterioration in "Physical Functioning", "Bodily Pain", "General Health", "Vitality" and "Social Functioning" subscales starting from 6th month, with statistically significant variations between 6th and 12th months (p=0.02, p=0.02, p=0.01, p=0.02, p=0.01, respectively). No statistically significant differences were noted in "Role-Emotional" and "Role-Physical" subscales (p=0.2, p=0.5, respectively).

In the SF-36 scale evaluation of the control group, a significant deterioration in "Physical Functioning", "Bodily Pain", "General Health" and "Social Functioning" subscales between baseline and at 12th month were encountered (p=0.02, p=0.04, p=0.02, p=0.03, respectively) (Table 2). It was observed that "Physical Functioning" and "General Health" subscales started to deteriorate by the 6th month in the control group (p=0.03, p=0.02, respectively). No statistically significant difference was noted in any of the other subscales.

DISCUSSION

The aim of CXL is to create new chemical bonds inside the corneal stroma tissue by application of riboflavin (vitamin B2) and ultraviolet A light (UVA, 370 nm). The light-induced production of oxygen radicals results in the formation of additional chemical bonds between collagen fibrils to induce stiffening of the cornea.[1-4] Although, the genesis aim of CXL procedure was the treatment of keratoconus, a role for CXL has also been suggested for other forms of corneal ectasia and a number of non-ectatic corneal diseases, such as infectious keratitis, bullous keratopathy, and corneal ulcers.[4]

Bullous keratopathy, caused by endothelial dysfunction, leads to chronic corneal edema, epithelial bullae, recurrent erosions, and subsequent visual impairment and ocular discomfort.[5] With the deterioration of the endothelial pump function, fluid accumulates in the extracellular spaces between the collagen fibers and lamellae. CXL re-

TABLE 1: SF-36 scores after CXL treatment.

	Pre-op	Post-op 1. month	Post-op 3. month	Post-op 6. month	Post-op 12. month	p
Physical Functioning	55.5±34.5 (70) (0-95)	65.5±30.2 (80) (15-100)	71.5±29.3 (85) (20-100)	73±24.2 (82.5) (25-100)	60±28.7 (70) (10-90)	**0.01**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			**0.01** **0.02** **0.04** 0.7 **0.02**
Bodily Pain	44.2±25.9 (43.7) (0-77.5)	61.2±31.6 (56.2) (0-100)	69.2±29.5 (72.5) (0-100)	69.2±27.7 (72.5) (0-100)	53.5±27.3 (56.2) (0-90)	**0.001**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			**0.05** **0.01** **0.01** 0.2 **0.02**
General Health	48±11.8 (45) (35-70)	48.5±15.1 (45) (35-80)	54.5±19.7 (47.5) (35-90)	56.5±17.6 (52.5) (35-90)	48±11.8 (45) (35-70)	**0.01**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			0.7 0.2 **0.04** 0.9 **0.01**
Vitality	50±13.7 (47.5) (35-80)	61±20.3 (55) (35-95)	64.5±16.4 (60) (45-85)	62.5±14.9 (60) (45-85)	51.5±11.3 (50) (35-75)	**0.002**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			**0.01** **0.01** **0.01** 0.5 **0.02**
Mental Health	60±19.4 (66) (28-80)	64.4±16.7 (68) (36-84)	72.4±14.5 (70) (52-96)	71.6±11.9 (70) (52-88)	58.4±14 (66) (36-72)	**0.003**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			0.2 **0.04** 0.06 0.5 0.1
Social Functioning	60±29.3 (62.5) (12.5-100)	60±29.3 (62.5) (12.5-100)	71.2±20.4 (68.7) (37.5-100)	82.5±17.8 (81.2) (50-100)	58.7±28.2 (50) (25-100)	**0.002**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month 6. month-12. month			0.09 0.08 **0.01** 0.1 **0.01**
Role-Emotional	30±36.6 (16.6) (0-100)	40±43.8 (33.3) (0-100)	50±45.1 (66.6) (0-100)	50±45.1 (66.6) (0-100)	30±39.9 (0) (0-100)	0.5
Role-Physical	30±36.8 (12.5) (0-100)	35±41.1 (12.5) (0-100)	35±41.1 (12.5) (0-100)	37.5±44.4 (12.5) (0-100)	30±34.9 (12.5) (0-75)	0.2

*It's showed that mean±SD values at the first line, median values at the second line and minimum-maximum values at he third line.

**p<0.05 was considered statistically significant and were showed in bold.

TABLE 2: SF-36 scores in the control group.

	Pre-op	Post-op 1. month	Post-op 3. month	Post-op 6. month	Post-op 12. month	p
Physical Functioning	80.5±31.2 (95) (0-100)	79±32 (95) (0-100)	76±31.9 (92.5) (0-100)	76.5±31.1 (90) (0-100)	75.5±31.1 (90) (0-100)	**0.01**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month			0.1 0.06 **0.03** **0.02**
Bodily Pain	41±21 (38.7) (12.5-67.5)	39±22.3 (33.7) (12.5-67.5)	39±23.5 (38.7) (0-67.5)	39±23.5 (38.7) (0-67.5)	30.2±31 (27.5) (0-67.5)	**0.01**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month			0.1 0.5 0.5 **0.04**
General Health	52±30.6 (62.5) (5-90)	52±27.8 (57.5) (10-90)	48.5±24.1 (55) (10-75)	46±26.5 (57.5) (5-70)	44±24.8 (57.5) (5-65)	**0.04**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month			1 0.3 **0.02** **0.02**
Vitality	53.5±19.4 (52.5) (10-85)	50±21.9 (47.5) (5-90)	51±24.2 (47.5) (0-90)	51±21.1 (50) (5-85)	49±14.6 (45) (25-80)	0.08
Mental Health	57.6±14.6 (58) (36-76)	54±16.9 (56) (28-76)	55.6±18.4 (56) (32-76)	53.2±19.7 (48) (20-80)	52.8±14.7 (48) (36-72)	**0.2**
Social Functioning	58.7±18.6 (62.5) (12.5-75)	62.5±16.6 (68.7) (25-75)	61.2±19.9 (68.7) (12.5-75)	61.2±19.9 (68.7) (12.5-75)	51.2±18.1 (56.2) (12.5-75)	**0.000**
			Pre-op-1. month Pre-op-3. month Pre-op-6. month Pre-op-12. month			0.08 0.1 0.1 **0.03**
Role-Emotional	50±52.7 (50) (0-100)	50±55.7 (50) (0-100)	50±53.6 (50) (0-100)	50±52.8 (50) (0-100)	50±53.4 (50) (0-100)	0.5
Role-Physical	42.5±47.2 (25) (0-100)	42.5±45.3 (25) (0-100)	42.5±47.4 (25) (0-100)	42.5±48.2 (25) (0-100)	42.5±46.4 (25) (0-75)	0.4

*It's showed that mean±SD values at the first line, median values at the second line and minimum-maximum values at the third line.

**p<0.05 was considered statistically significant and were showed in bold.

duces this corneal edema by inducing more concentrated cross-linked fibers and reducing possible gaps for fluid accumulation.[5-8] Bullous keratopathy is one of the leading indications for keratoplasty all over the world.[6,9] Although, the main indication for keratoplasty in these patients is visual loss due to hazy cornea, the secondary indication for keratoplasty is the disabling pain that restricts their daily life. Bursting of epithelial bullae causes significant pain, tearing and conjunctival hyperemia by leading corneal nerve endings to expose.[10] CXL offers an alternative approach for reducing ocular pain by limiting the occurrence of macro- and microbullae. Due to these potential utilities, CXL has been suggested as a promising alternative method in managing bullous keratopathy by re-

ducing ocular discomfort, increasing visual acuity and probably postponing or even eliminating the need for corneal transplantation.[5-7]

As pain is one of the most important human senses, it is almost the most common complaint in clinical practice. Pain is accepted as a complex interaction including physical, behavioral, emotional and cognitive dimensions.[11] Persons react differently to pain, moreover their pain durability and accepting that pain may also vary. It may be considered that all of this reflect on their quality of life.[12] Having negative cognitions, affect the emergence of pain, such as playing a role in the perception of pain, pain severity and quality of life.[13] The course of pain and quality of patients heal by the development of positive and effective cognitions, and starting to use appropriate dealing ways.[12,14]

Recently, assessing quality of life with general purpose or disease spesific questionnaires has become popular. Health-related quality of life is defined as "health included physical, psychological and social areas that are affected by different areas such as person's experiences, beliefs and expectations". Health-related quality of life is important for measuring the impact of the diseases to persons lives.[15] Short Form 36 (SF-36) is a general purpose quality of life scale that provides extensive measurements.[16] The scale is easy to apply and it has a wide range of use.[17]

Herein, we used SF-36 questionnaire evaluating the general quality of life scale for all patients. One of the most important features of this scale is its self-evaluation format. Moreover, it can be completed within five minutes, and both negative and positive aspects of health status can be evaluated with this test.[18] The questionnare consists of 36 items which assess eight health concepts: physical functioning (PF-10 items), role limitations due to physical problems (RP-4 items), bodily pain (BP-2 items), general health perception (GH-5 items), vitality (VT-4 items), social functioning (SF-2 items), role limitations due to emotional problems (RE-3 items), and mental health (MH-5 items).[16] These 35 items evaluate the last 4 weeks of the person. SF-36 also includes one more item-which is not used in the measurement-that assess changes in respondent's health status during the past year.[16] Extensive background information on the SF-36, as well as standard scoring algorithms and interpretation guides are available in the literature.[4,18] For each tested quality of life domain, item scores are coded, summed, and transformed into a scale from 0 (worst) to 100 (best) using the standard SF-36 scoring algorithms.[18] SF-36 was translated into Turkish and validation studies of Turkish version of SF-36 were carried out in 1999 by Kocyigit et al.[19]

To the best of our knowledge, no publication in the literature has ever evaluated patients with bullous keratopathy during 1 year with an objective quality of life scale, such as SF-36. In 2008, Krueger et al performed CXL on a patient with advanced bullous keratopathy for the first time, and reported that a follow up of 6 months demonstrated a pain decrease in the patient.[7] In another study, CXL was performed in 3 patients with bullous keratopathy and the bullous changes of the epithelium markedly improved in the following 8 months, resulting in loss of pain and discomfort in all patients.[5] However, no objective evaluation scale was used in neither of these studies.[5,7]

Ghanem et al performed CXL on 14 painful patients with pseudophakic bullous keratopathy and used "National Pain Education Council" for the measurement of ocular pain intensity. They reported a significant reduction in pain scores at the first month, but this improvement declined and returned back to baseline values by the 6th month.[6] After CXL treatment, the scores for "Physical Functioning", "Vitality", and "Bodily Pain" subscales improved significantly, however distinct from Ghanem et al's study, these improvements started at the 3rd month and continued up to the 6th month.

The earlier improvement in "Physical Functioning" and "Vitality" subscales than "Bodily Pain" subscale might be caused by the psychological relaxation related to receiving a treatment during this time. Similar to "Bodily Pain" subscale, "Mental Health" subscale also improved at the 3rd month. However, "General Health" and "Social Function-

ing" subscales improved by the 6th month. This improvement delay in these subscales might be related to the warily approach after the treatment. The earlier higher scores for "Mental Health" subscale support the effect of pain on mental health. The deterioration in "Physical Functioning", "Bodily Pain", "General Health", "Vitality" and "Social Functioning" subscales after 6 months, goes along with the temporariness of the treatment.

In the control group, a significant deterioration in "Physical Functioning", "Bodily Pain", "General Health" and "Social Functioning" subscales between baseline and 12 months after was determined. These results promote the quality of life getting worse in the course of bullous keratopathy.

Some studies report that in patients with bullous keratopathy CXL treatment might induce an increase in BCVA.[6,7,20] Ghanem et al. observed an increase in BCVA at first month, but there was no difference between the 6th month and baseline values.[6] Kozobolis et al. also observed a significant improvement in BCVA, in two patients with bullous keratopathy and ulcerative keratitis after CXL treatment.[20] Kruger et al. reported one case with a significant improvement in BCVA at the 6th month of CXL treatment.[7] However, we detected no significant difference in BCVA of the treated patients.

The results of this study support that CXL is succesful in the symptomatic treatment of bullous keratopathy by temporarily improving the quality of life. CXL may be useful in the treatment of bullous keratopathy when waiting for keratoplasty, particularly in patients with intense pain.

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