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The Effect of Coenzyme Q_{10} Eye Drop on Corneal Wound Healing in the Treatment of Bacterial Keratitis: A Prospective Clinical Study

Bakteriyel Keratit Tedavisinde Koenzim Q_{10} Göz Damlasının Korneal Yara İyileşmesi Üzerine Etkisi: Prospektif Klinik Çalışma

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ABSTRACT Objective: We aimed to evaluate the effectiveness and safety of Coenzyme Q_{10} (CoQ_{10}) eye drops on corneal wound healing in bacterial keratitis. **Material and Methods:** Patients who were hospitalized and treated for bacterial keratitis were included in the study. The age, gender, and the affected eyes of the patients were recorded. The patients underwent a complete ophthalmologic examination and the presence or absence of hypopyon was recorded. The size of the corneal ulcer was measured horizontally and vertically. Patients were randomly divided into 2 groups. Both groups received topical antibiotics and cyclopentolate drops. In addition to the first group, CoQ_{10} eye drop 4×1 treatment was added. Corneal ulcer images were taken before the treatment and recorded daily after the treatment initiation, until the ulcer healed. **Results:** The mean age of the 32 patients included in the study was 51.16±25.31 (7-90) years, 20 (62.5%) were male and 12 (37.5%) were female. There was no statistically significant difference in terms of age, gender, right and left eye involvement, hypopyon presence and corneal ulcer size in CoQ_{10} eye drop group (n=16) and control group (n=16) (p>0.05). The mean healing time was 12.25±6.02 days in CoQ10 eye drop group and 19±12.9 days in control group (p=0.076). **Conclusion:** The effect of CoQ_{10} eye drops in the treatment of bacterial keratitis with corneal ulcers was not found to be statistically significant. However, it can be considered as an adjuvant agent in terms of shortening the healing time. There is a need for more extensive series, randomized, prospective clinical trials.

Keywords: Corneal ulcer; keratitis; Coenzyme Q_{10}

ÖZET Amaç: Bu çalışmada, bakteriyel keratitte Koenzim Q_{10} (KoQ_{10}) göz damlasının korneal yara iyileşmesi üzerindeki etkinliğini ve güvenilirliğini değerlendirmeği amaçladık. **Gereç ve Yöntemler:** Bakteriyel keratit tanısıyla yatırılarak tedavisi yapılan hastalar çalışmaya alındı. Hastaların yaşı, cinsiyeti ve hangi gözün tutulduğu kaydedildi. Hastalara tam bir göz muayenesi yapıldı ve hipopiyon olup olmadığı kaydedildi. Korneal ülser büyüklüğü yatay ve dikey olarak ölçüldü. Hastalar rastgele 2 gruba ayrıldı. Her iki gruba da topikal antibiyotik ve siklopentolat damla verildi. Birinci gruba ek olarak KoQ_{10} göz damlası 4×1 tedaviye eklendi. Tedavi öncesi ve tedaviye başlandıktan sonra ülser iyileşene kadar günlük olarak korneal ülser görüntüleri alındı ve kaydedildi. **Bulgular:** Çalışmaya alınan toplam 32 hastanın yaş ortalaması 51,16±25,31 (7-90) yıl olup, 20'si (%62,5) erkek, 12'si (%37,5) kadın idi. KoQ_{10} göz damlası verilen grup (n=16) ile kontrol grubunun (n=16) yaş, cinsiyet, sağ-sol göz tutulumu, hipopiyon varlığı ve korneal ülser boyutu açısından istatistiksel olarak anlamlı farkı yoktu (p>0,05). Ortalama iyileşme süresi KoQ_{10} göz damlası verilen grupta 12,25±6,02 gün ve kontrol grubunda 19±12,9 gün idi (p=0,076). **Sonuç:** KoQ_{10} göz damlası, bakteriyel keratite bağlı gelişen korneal ülser tedavisindeki etkisi istatistiksel olarak anlamlı bulunamadı. Ancak iyileşme süresinin kısalması açısından adjuvan ajan olarak düşünülebilir. Bu konuda daha geniş serilere sahip randomize, prospektif klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Korneal ülser; keratit; Koenzim Q_{10}

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Corneal ulcer is sight-threatening severe condition with severe pain. The cause of corneal damage can be mechanical, biological, chemical or radial. Infective keratitis is one of the most important cause of low vision and blindness in the world.[1] Infective keratitis is generally caused by bacterial, fungal and viral agents. Among these, bacterial keratitis is the most common.[2]

Topical antibiotics are the first treatment option in bacterial keratitis. In a recently published review it has been emphasized that all of the commonly used topical antibiotics are equally effective.[3] In keratitis, the development of corneal melting, scar and perforation, starting with corneal ulcer, causes functional and anatomically poor results and may require keratoplasty. In the treatment of keratitis, corneal ulcer healing and diminution in size indicate the effectiveness of the treatment. For this reason, one of the targets of keratitis treatment is early recovery of corneal ulcer. Effective and early treatment positively affects the prognosis.

Factors such as apoptosis (programmed cell death) in the corneal cells, necrosis, cytokines that trigger extracellular tissue damage, oxidants and free radicals play a role in the development and progression of ulcers. The healing process of corneal ulcers is a serious problem, especially in resistant ulcers. Some treatment-resistant cases may not fully recover.[4]

Some medicines can help heal the cornea after corneal epithelial damage and regulate the healing process.[5] One of these drugs, Coenzyme Q_{10} (CoQ_{10}), is found in biological membranes and specifically functions in mitochondrial electron transport complex I (NADH-ubiquinone oxidoreductase), II (succinate-ubiquinone oxidoreductase) and III (ubiquinone-cytochrome oxidoreductase).[6] In some recent studies, CoQ_{10}, a potent antioxidant and anti-inflammatory agent, has been shown to inhibit apoptosis and thus reduce tissue destruction. It was shown that the use of CoQ_{10} in ophthalmology provides preservative support against harmful free radicals after refractive surgery, inhibits corneal keratocyte apoptosis caused by excimer laser, reduces the cell apoptosis in cornea exposed to ethanol before treatment.[7-11]

In a recently published study, CoQ_{10} has been shown in vivo and in vitro to reduce corneal damage after ultraviolet B exposure. In the same study, it was shown that CoQ_{10} supports corneal wound healing after corneal epithelial debridement in rabbits.[12]

In our literature search, we did not find a randomized, controlled clinical trial evaluating the effect of CoQ_{10} in corneal ulcer treatment in humans. We aimed in our study to evaluate the efficacy and safety of CoQ_{10} eye drops in patients with bacterial keratitis by comparing them with the standard treatment group.

MATERIAL AND METHODS

Study included patients admitted for bacterial keratitis to Van Yüzüncü Yıl University Ophthalmology Department. Cases of suspected bacterial keratitis in the eye examination and without previous medical or surgical treatment were included in the study. Cases with Herpes simplex, acanthamoeba or fungal keratitis, physical or chemical injuries and non-infectious keratitis were not included in the study.

This prospective study was carried out following approval of the Clinical Researches Ethics Committee (date: November 13, 2014; number: 04). Recruited patients were informed about the study and signed the informed consent form. This study was carried out in line with the principles of the Helsinki Declaration.

Age, sex, and involved eye of each patient were recorded. After receiving the medical history, the best corrected visual acuity was obtained and a full eye examination was performed. It was recorded whether hypopyon is present. The size of corneal ulcer was measured using biomicroscopy (TOPCON Slit Lamb SL D7, Tokyo, Japan). Localization of keratitis was classified in 5 regions; central, upper, lower, nasal and temporal regions. Cases with an ulcer depth less than 1/3 of the corneal thickness were included in the study. All cases were sampled for culture and gram staining from the lesion site. Patients were randomly divided into 2 groups. Both groups received one drop per hour of fortified Cefazolin 50 mg/mL (Prepared from Sefazol vial, Gensenta, Turkey) and one drop per hour of fortified Gentamicin 14 mg/mL (Prepared

from Genta ampoule, Menarini, Turkey), one drop three times a day of cyclopentolate. In addition to the first group, CoQ_{10} (Visudrop, Visufarma, Italy) eye drop 4x1 was added to treatment and used for at least 2 weeks or until keratitis is recovered. In this study, the main aim was to closure the epithelial defect, which is one of the most important healing symptoms of corneal ulcers. The healing process was photographed and recorded daily using normal and cobalt blue filter before treatment and after the treatment was initiated [imaging biomicroscopy, TOPCON SL D7 (DC-3) IMAGEnet i-base ver. 3.13.1, Tokyo-Japan] (Figure 1).

STATISTICAL ANALYSIS

Descriptive statistics were presented as mean and standard deviation for the continuous variables, while count and percentages for the categorical variables. Mann-Whitney U test was used to compare control and CoQ_{10} groups. Fisher's exact probability tests were used for comparison of 2 proportions of the groups. Statistical significance level was considered as 5%. MINITAB (Ver:14, Informer Technologies, Inc., USA) and SPSS (Ver: 13, IBM inc, USA) statistical programs were used for all statistical computations.

RESULTS

The age average of 32 patients included in the study was 51.16±25.31 (7-90) years and 20 (62.5%) of them were male and 12 (37.5%) were female. Culture positivity was detected in 14 (43.75%) cases. *Staphylococcus aureus* was detected in 5 (35.71%), *Streptococcus pneumoniae* in 4 (28.57%), *Staphylococcus epidermidis* in 2 (14.29%), *Pseudomonas aeruginosa* in 2 (14.29%) and *Haemophilus influenzae* in 1 (7.14%) of those cases.

CoQ_{10} eye drop group (n=16) and the control group (n=16) were intercompatible in terms of age average, gender, involved eye and the presence of hy-

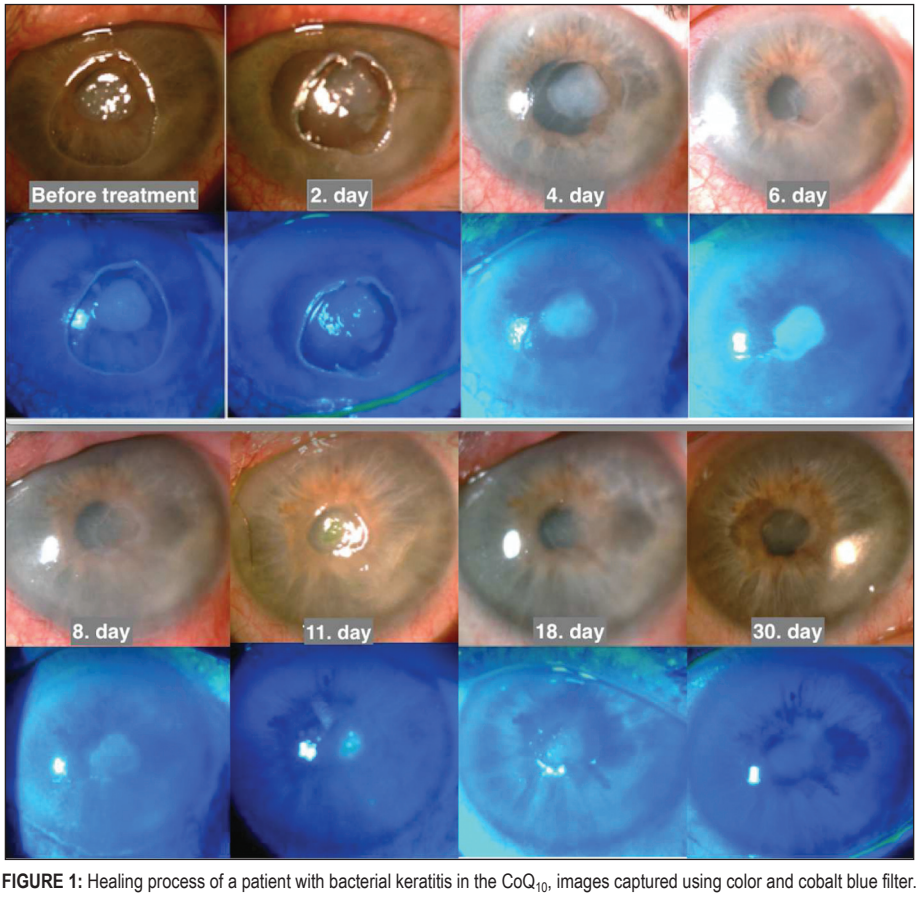

FIGURE 1: Healing process of a patient with bacterial keratitis in the CoQ_{10}, images captured using color and cobalt blue filter. CoQ_{10}: Coenzyme Q_{10}.

TABLE 1: Distribution and general characteristics of patients according to groups.

	CoQ_{10} (n=16)	Control (n=16)	p value
Age average[a]	46.06±26.42	56.6±23.72	0.235
Gender (male/female)[b]	10/6	10/6	1
Right/left eye involvement[b]	7/9	8/8	0.723
Presence of hypopyon[b]	7 (43.75%)	5 (31.25%)	0.461

[a]Mann-Whitney U test; [b]Fisher's exact probability tests; CoQ_{10}: Coenzyme Q_{10}.

TABLE 2: Properties and healing duration of bacterial keratitis.

	CoQ_{10} (n=16)	Control (n=16)	p value
Size of ulcer[a]			
Horizontal (mm)	3.42±1.95	2.91±1.96	0.354
Vertical (mm)	2.95±1.64	2.62±1.05	0.691
Average healing duration (days)	12.25±6.02	19±12.9	0.076
Ulcer location[b]			
Central	11	5	0.022
Inferior	2	3	0.625
Superior	1	2	0.542
Nasal	1	4	0.333
Temporal	1	2	0.542
Average BCVA (logMAR)[a]			
Before treatment	1.81±1.07	1.93±1.12	0.754
After treatment	1.55±1.2	1.08±1.14	0.326

[a]Mann-Whitney U test; [b]Fisher's exact probability tests; CoQ_{10}: Coenzyme Q_{10}; BCVA: Best corrected visual acuity.

popyon (Table 1). Corneal ulcer sizes and pre-treatment best corrected visual acuity were also coherent with each other. The mean duration of recovery was not statistically significant, but in the CoQ_{10} group healing happened about 7 days earlier on average. Regarding culture positive cases, the recovery time was 6.67 (mean rank) days in the gram negative bacteria and 7.73 (mean rank) days in gram positive ones (p=0.695). Statistical analysis is considered to have low reliability due to difference in case numbers in the 2 groups. Antibiogram results based on growth in culture were sensitive to the treatment given. There was no significant difference in mean post-treatment best corrected visual acuity (Table 2). No treatment-related side effects and complications were observed in our study.

DISCUSSION

New alternative methods that can be more effective in the treatment of corneal ulcers and reduce the duration of treatment are needed. We evaluated in our study the effect of CoQ_{10} drop, which is one of these methods, on the duration of healing of bacterial keratitis. In our results, the effect of CoQ_{10} eye drops in the treatment of bacterial keratitis with corneal ulcers was not found to be statistically significant. However, we found that the corneal ulcers healing time was shorter in the group given CoQ_{10} eye drops compared to the control group.

CoQ_{10} has many useful functions for ocular cells and has gained importance in ophthalmology in recent years.[12-14] CoQ_{10}, a potent antioxidant and anti-inflammatory agent, prevents apoptosis and thus reduces tissue destruction. In addition to the mitochondrial bioenergetic effect of CoQ_{10}, it also prevents the oxidative damage of free radicals in mitochondrial and lipid membranes.[15]

The best treatment for bacterial keratitis is topical antibiotics.[1] In our study, fortified Cefazolin 50 mg/mL and fortified gentamicin 14 mg/mL were used

as topical antibiotics for both groups. Studies have shown that drop-fortified aminoglycosides and fortified cephalosporin drops are effective in bacterial keratitis.[1,16] Cross-linking collagen using ultraviolet-A and riboflavin may be effective for medical treatment-resistant bacterial keratitis.[17]

In addition to topical antibiotic treatment, we applied one drop of CoQ_{10} 4 times a day to the first group. This ophthalmic solution contains CoQ_{10} plus vitamin E-tocopheryl polyethylene glycol succinate (E-TPGS) 500 mg and hypromellose (Visudrop; Liba Laboratories, Inc.). Vitamin E-TPGS increases the ability of active ingredients to reach the target tissue as well as its antioxidant effect. Hypromellose is a kind of eye moisturizer that improves the exposure of the ocular surface as well as its moisturizing properties.

In a recent study, the treatment effect of CoQ_{10} eye drops in 6 difficult cases who were not recovered by conventional treatment of corneal ulcer was evaluated. There were 3 cases of neurotrophic corneal ulcer, 2 cases of post-infection corneal ulcer (1 acanthamoeba keratitis and 1 case of unknown keratitis), 1 case of Stevens-Johnson syndrome and 1 drop 3-4 times a day of CoQ_{10} was added to preservative-free topical treatments. All cases were completely healed with the addition of CoQ_{10}. In 4 cases, treatment response was received within 1-2 weeks and completely recovered within 4-8 weeks. No side effects were detected in this case series.[4]

The therapeutic effect and potential mechanism of CoQ_{10} in corneal ulcers can be explained in 3 ways. First, reactive oxygen species and ocular surface inflammation can prevent corneal healing. Antioxidant and anti-inflammatory effects of CoQ_{10} eye drops can contribute to the healing of corneal ulcer. Secondly, increased energy is needed at every step of corneal wound healing. CoQ_{10} drops can contribute to wound healing by providing mitochondrial bioenergy. Third, CoQ_{10} drop repairs the corneal subbasal plexus and can contribute to the faster healing of the corneal wound.[18]

Our study had a few limitations. First, our case count is low. Secondly, corneal lesions are not standardized in terms of characteristics such as size and depth. Although there is no statistically significant difference in these characteristics in our study, these parameters may have an effect on the results. The same standards can be provided for animal studies, but it is difficult to provide the same standards in patients. Finally, there are keratitis related corneal ulcers that can be caused by different factors and of which the exact cause is unknown. In a published review, positive culture yield for infective keratitis were reported as 51% (34-67%) and positive Gram stain yield as 67% (60-75%).[19] The low rate of positive culture may be associated with several factors such as diagnostic variability, the skill of the sampling operator, culture technique.

CONCLUSION

CoQ_{10} eye drop may be considered as an adjuvant agent that shortens the healing period and promotes corneal wound healing in bacterial keratitis but the effect is not found to be statistically significant. However, there is a need for randomized, prospective clinical trials including larger series.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Muhammed Batur;* ***Design:*** *Muhammed Batur;* ***Control/Supervision:*** *Muhammed Batur, Erbil Seven;* ***Data Collection and/or Processing:*** *Muhammed Batur, Muhammet Derda Özer, Serek Tekin;* ***Analysis and/or Interpretation:*** *Muhammed Batur, Erbil Seven;* ***Literature Review:*** *Muhammed Batur, Muhammet Derda Özer;* ***Writing the Article:*** *Muhammed Batur, Serek Tekin;* ***Critical Review:*** *Muhammed Batur;* ***References and Fundings:*** *Muhammed Batur, Erbil Seven;* ***Materials:*** *Muhammed Batur, Serek Tekin.*

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