Corneal Endothelial Damages After Abuse of Topical Proparacaine: Case Report

Topikal Proparakain Kötü Kullanımı Sonrası Gelişen Kornea Endotel Hasarı

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ABSTRACT A 36-year-old male presented to clinic complaining of pain in the right eye. Biomicroscopy revealed corneal erosion, corneal edema, and ring-shaped stromal infiltration. The patient had abused proparacaine for an extended period of time; thus, we attributed these clinical findings to toxic keratopathy. The patient was treated with topical antibiotic and cycloplegic, pending the results of the antibiogram. On the fourth day of treatment, upon receipt of negative culture results and the completion of corneal epithelization, topical steroid were added. Corneal endothelial cell analyses performed after the medical treatment and cornea became transparent revealed a reduction in the endothelial cell density, polymorphism and polymegatism. Topical proparacaine abuse may cause permanent damage to the corneal endothelium in addition to its known effects on the corneal epithelium and stroma.

Key Words: Corneal ulcer; corneal endothelial cell loss

ÖZET 36 yaşında erkek hasta sağ gözde ağrı yakınması ile başvurdu. Biomikroskop ile yapılan oftalmolojik muayenede kornea erozyonu, kornea ödemi ve halka şeklinde stromal infiltrasyon görüldü. Sol göz biomikroskopisi normaldi. Hastanın öyküsünden uzun süre proparakain damla kullandığı öğrenildi. Bu öykü ve biomikroskopik bulgular ile hastaya toksik keratopati tanısı kondu. Hastanın kültür antibiogram sonuçları beklenirken topikal antibiyotik ve sikloplejik damla başlandı. Tedavinin dördüncü gününde, korneal epitelizasyonun tamamlanması ve kültür sonuçlarının negatif gelmesiyle tedaviye topikal steroid eklendi. Tıbbi tedavinin tamamlanması ve korneanın şeffaflaşması sonrasında hastanın her iki gözüne de korneal endotel hücre analizi uygulandı. Sağ gözde endotel hücre yoğunluğunda azalma, polimorfizm ve polimegatizm saptandı. Topikal proparakainin kötü kullanımının kornea epiteli ve stroması üzerine bilinen yan etkilerine ek olarak kornea endotelinde de kalıcı hasara neden olabildiği sonucuna ulaşıldı.

Anahtar Kelimeler: Korneal ülser; korneanın endotel hücre kaybı

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Topical anesthesia is frequently used in ophthalmology during examinations and surgical procedures. Common topical anesthetics include proparacaine, tetracaine, and oxybuprocaine. To our knowledge, side effects related to the routine ophthalmologic use of these substances have not been reported. However, changes occurring at the conjunctiva, cornea, and the anterior chamber due to abuse by patients have been known to occur and are defined as "toxic keratopathy." Clinical findings related to toxic keratopathy include punctate epithelial ke-

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ratopathy, persistent epithelial defect, Wessely immune ring–like infiltration or disciform stromal infiltration, stromal edema, and Descemet folds.[1,2] We present our findings and the results of treatment of a patient who had corneal endothelial changes resulting from toxic keratopathy due to proparacaine abuse.

CASE REPORT

A 36-year-old male patient came to our clinic complaining of pain in the right eye. The patient was a welder who had had an iron chip in his right eye 1 month earlier. Although this foreign body was removed from his eye by an ophthalmologist, the patient's pain did not decrease. The patient used 0.5% topical proparacaine (Alcaine, Alcon Belgium) excessively (approximately 4 bottles- per bottle contain 15 ml), due to continuing pain in his eye. The pain did not disappear despite the use of topical proparacaine, and the patient had begun to experience reduced vision by the time he was seen by us.

Ophthalmologic examination revealed that the patient's visual acuity was 0.05 in the right eye and 1.0 in the left eye. Biomicroscopy of the right eye revealed total corneal erosion, dense stromal edema, ring-shaped corneal infiltration, Descemet folds, and +1 tyndall in the anterior chamber (Figure 1). No pathology was found in the left eye. Samples obtained from the patient's conjunctiva and cornea were sent to microbiology.

The patient was treated with topical antibiotic (ofloxacin 0.3%, 8 times per day) and cycloplegic (cyclopentolate 1%, 2 times per day), pending the results of the antibiogram. On the fourth day of treatment, upon receipt of negative culture results and the completion of corneal epithelization, topical steroid (dexamethasone alcohol, 0.1%, 4 times per day) was added. Medical treatment continued with the drop dosages adjusted. The patient's corneal edema receded in approximately 1 month.

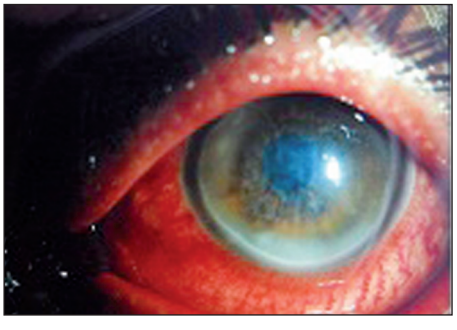

FIGURE 1: Biomicroscopic image of the right eye in the first examination.

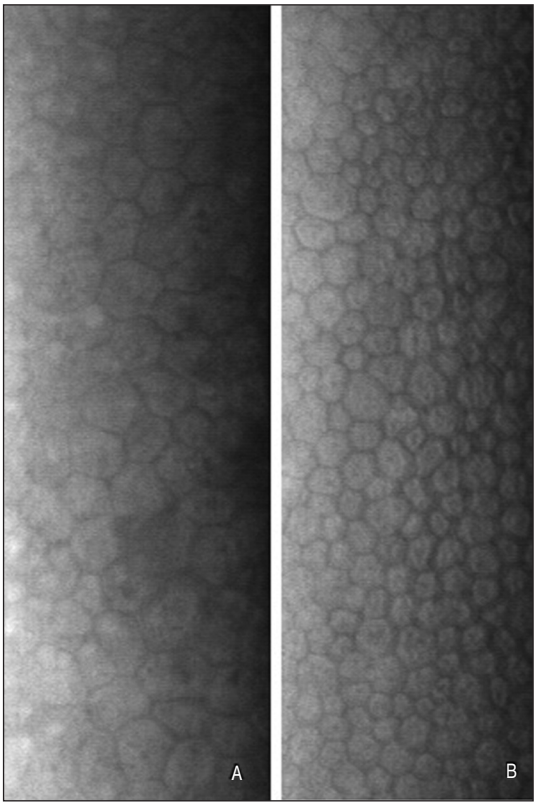

FIGURE 2: Central endothelial image of the right **(A)** and left **(B)** cornea.

At the end of the first month, visual acuity was 0.5 in the right eye and 1.0 in the left eye. The cornea of the right eye was transparent upon biomicroscopy. Images of the central corneal endothelium were obtained from both of the patient's eyes with an SP-2000P (Topcon Corp., Tokyo, Japan) non-contact specular microscope (Figure 2). The clearest image was selected from among three images and subjected to automatic cell analysis with ImageNET. The endothelial cell analysis revealed the cell density, hexagonality, and coefficient of variance of cell size. The results from both eyes are presented in Table 1. The endothelial cell density was 1,301 cell/mm^2 for the right eye, and 2.815 cell/mm^2 for the left eye (Table 1).

TABLE 1: Endothelial cell analysis of the patient's right and left corneas.

Eye	Cell density (cell/mm^2)	Hexagonality	Coefficient of variance of cell size (%)
Right	1.301	50%	45.9%
Left	2.815	63%	38.0%

DISCUSSION

Permanent changes occurred in the corneal endothelium of this patient, who had toxic keratopathy after proparacaine abuse; however, the clinical findings improved following treatment.

Although corneal endothelial changes are considered to be among the symptoms of toxic keratopathy, the literature regarding this subject is limited. To our knowledge, the first report of toxic keratopathy associated with topical anesthetics was published by Weekers, who investigated the effects of cocaine, lidocaine, and benoxinate on the corneal epithelium of rabbits.[3] He suggested that topical anesthetics increased the osmotic pressure by causing changes in the Na^+/K^+ endothelial pump, leading to stromal hydration.

To investigate the endothelial toxicity of topical anesthetics in pigmented rabbits, Judge et al.[4] injected either 0.75% bupivacaine HCl, 4% unpreserved lidocaine HCl, 0.5% proparacaine HCl, or 0.5% tetracaine HCl into the anterior chamber of one eye and the same amount of balanced salt solution into the other eye. They then investigated the subsequent changes in central corneal thickness and transparency. On days 1, 3, and 7 post-injection, there were statistically significant increases in the thickness and opacification of the cornea in the eyes that were injected with bupicacaine, lidocaine, or proparacaine, while no statistically significant differences were observed in the eyes injected with balanced salt solution injection or tetracaine.

Risco and Millar found central corneal scarring and thinning of the cornea in a patient who developed a corneal scar due to oxybuprocaine abuse; their case report presents the results of scanning electron microscopic and transmission electron microscopic investigations.[5] Endothelial polymorphisms, focal endothelial necrosis, and numerous filamentous processes extending to the abnormally diluted intercellular spaces were observed in the scanning electron micrographs, and reduced-to-absent apical cell connections were found at the endothelial intercellular junction in the transmission electron micrographs.

Grant and Acosta compared the toxicity of topical anesthetics in primary cultures of rabbit corneal epithelial cells.[6] They found that tetracaine was more toxic than proparacaine in their in vitro experiments. Moreira et al. investigated the impact of anesthetics on keratocytes by incubating human keratocyte cultures with various topical anesthetics.[7] They determined that both tetracaine and proparacaine decrease keratocyte viability and concluded that this effect was associated with the length of exposure rather than concentration.

The results of the aforementioned studies indicate that topical anesthetics are toxic to the corneal epithelium, stroma, and endothelium. Proparacaine drops contain 0.5% proparacaine HCl and 0.01% benzalkonium chloride. It is not entirely clear whether it is the active substance or the preservative that is causing the toxic keratopathy. However, anesthetics without preservatives have been shown to have toxic effects on the endothelium , and benzalkonium chloride is also known to be associated with endothelial toxicity; thus, these two substances may act synergistically to cause toxic keratopathy.[4]

To the best of our knowledge, there have been no in vivo clinical studies showing that endothelial damage is caused by toxic keratopathy. In this patient, after treatment to return the cornea to transparency, we determined that there was a reduction in the endothelial cell density, as well as polymorphism and polymegatism; we believe that these clinical findings were associated with topical anesthetic abuse.

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