Ring Keratitis Associated With Topical Abuse of a Dilute Anesthetic After Refractive Surgery

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Anesthetic toxic keratitis is rare and presents as a ring keratitis, which is often misdiagnosed as *Acanthamoeba* keratitis. Here, we report an unusual case of toxic keratitis caused by topical abuse of a dilute anesthetic. A 26-year-old woman presented with bilateral corneal edema, ring infiltrates, pigmented keratic precipitate, Descemet's membrane folding, and strong anterior chamber reactions 2 weeks after laser subepithelial keratomileusis surgery. Tracing back her medical history, topical dilute 0.1% proparacaine was prescribed and frequently used for 1 month. Toxic keratitis was suspected. After discontinuation of the topical anesthetic and initiation of treatment with topical 20% autologous serum, complete corneal epithelialization was achieved within 1 week. Vision improved from finger counting to 20/20 in the right eye and 20/25 in the left eye, but confocal microscopy showed decreased corneal endothelial cells. Topical abuse of a dilute topical anesthetic can cause severe toxic keratitis and endothelial cell loss. The physician must be aware of the signs of topical anesthetic abuse and should not prescribe even a dilute anesthetic for long-term use. Autologous serum can help in the recovery of toxic keratitis. [J Formos Med Assoc 2009;108(12):967–972]

**Key Words:** autologous serum, endothelial cell loss, topical anesthetic abuse, toxic keratitis

Toxic keratitis caused by topical abuse of anesthetics is rare but can result in severe keratopathy, including persistent epithelial defect, Wessely-type immune ring infiltration, disciform stromal edema, Descemet's membrane folding, and even hypopyon.1–4 More serious is secondary infectious keratitis or possible misdiagnosis as *Acanthamoeba* keratitis caused by ring keratitis.3,4 We report a case of bilateral toxic keratitis associated with abuse of topical dilute 0.1% proparacaine after laser subepithelial keratomileusis (LASEK) surgery. After the prompt cessation of topical proparacaine and initiation of treatment with topical diluted 20% autologous serum, complete corneal epithelialization was achieved within 1 week, and the patient finally had good visual recovery.

**Case Report**

A 26-year-old woman had bilateral high myopia and wore soft contact lenses for 8 years. She underwent bilateral LASEK surgery with 0.02% mitomycin C (MMC) soaking for 2 minutes. Bandage contact lenses were applied to both eyes at the end of surgery. Topical 0.3% ciprofloxacin and 0.1% fluorometholone four times daily were given. One week postoperatively, the bandage contact lenses were removed after complete corneal
epithelialization. Unfortunately, corneal epithelial defects and some peripheral infiltrates developed in both corneas 2 weeks postoperatively. She felt pain and experienced photophobia. Bandage contact lenses were applied again and topical 25 mg/mL amikacin and diclofenac four times daily were given. However, corneal epithelial defects and edema still increased, and topical 1% prednisolone four times daily was added. Then, peripheral infiltrates progressed to a ring shape in both corneas. Numerous keratic precipitates and marked anterior chamber reaction were also noted 4 weeks postoperatively. As a result of severe eye pain and ring keratitis, she was referred to our hospital with suspicion of *Acanthamoeba* keratitis.

On initial examination, she presented with bilateral severe eye pain and photophobia. The patient’s vision was evaluated by finger counting at 50 cm in both eyes. Both eyelids were edematous, and the conjunctiva was severely hyperemic. Slit-lamp biomicroscopic examination showed an 8 × 8-mm disciform central corneal epithelial defect, peripheral ring infiltrates, and diffuse stromal edema in both eyes (Figures 1A and 1B). There was marked folding in Descemet’s membrane and numerous fine-pigmented keratic precipitates, with a strong anterior chamber reaction (Figure 1C). Toxic keratitis was suspected. Tracing back the patient’s medical history, topical dilute anesthetic with 0.1% proparacaine was prescribed for use as necessary to relieve eye pain after LASEK surgery. The patient actually used the proparacaine every 15 minutes for 1 month because of frequently intolerable pain. The topical 0.1% proparacaine was refilled several times in the clinic. Anesthetic abuse keratopathy was diagnosed. Scraping smear examinations of both corneas showed numerous polymorphonuclear cells without any pathogens. Corneal cultures of bacteria, fungi, *Acanthamoeba* and viruses were performed on both eyes. Later, all cultures produced negative results except for small growth of *Staphylococcus epidermidis* from the right eye, which might have been caused by contamination. All the previously prescribed topical medications were discontinued. The patient was treated with topical

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Figure 1. (A, B) Slit-lamp biomicroscopic examination shows a large central epithelial defect and ring-shaped infiltrates in the right and left eye, respectively. (C) Numerous pigmented keratic precipitates deposited on Descemet’s membrane, which shows signs of folding.
sulfamethoxazole and preservative-free lubricant four times daily, and 20% autologous serum hourly. Autologous serum was prepared from a total of 20 mL of the patient’s blood obtained by venipuncture. The container was left standing for 2 hours at room temperature to ensure complete clotting, and was centrifuged at 1500 rpm for 15 minutes. The supernatant serum was carefully separated under sterile conditions and diluted by normal saline to a concentration of 20%. It was finally added to a 5-mL bottle and kept in a refrigerator. Oral diclofenac, 75 mg daily, was also added to reduce eye pain. After treatment with autologous serum, photophobia and eye pain quickly reduced. Complete corneal epithelialization was achieved within 1 week and corneal infiltrates were much reduced. Then, preservative-free 0.1% betamethasone was added four times daily. Corneal edema and anterior chamber reaction gradually diminished. After 2 weeks of treatment, her eye pain and photophobia disappeared, and the best-corrected visual acuity (BCVA) recovered to 20/100 in both eyes. Confocal microscopy (ConfoScan 3; Nidek Inc., Fremont, CA, USA) showed decreased central corneal endothelial cell density to 2128 cells/mm² in the right eye and 1024 cells/mm² in the left eye. Marked pleomorphism and polymegathism occurred in the endothelial cells and some highly reflective deposits are observed. Nuclei of endothelial cells were more prominent in the left than the right eye.

Discussion

Topical 0.5% proparacaine is used commonly during refractive surgery, but it is unusual to
prescribe diluted proparacaine for the management of pain after excimer photokeratectomy. The early presenting signs of topical anesthetic abuse include persistent epithelial defects and stromal infiltrate.\textsuperscript{1,2} Ring infiltration, keratic precipitates, and endothelial loss can occur within days to weeks of onset. Furthermore, the signs and symptoms related to topical anesthetic abuse can masquerade as \textit{Acanthamoeba} keratitis because of similarities such as disproportionate pain, use of bandage contact lenses, and corneal ring infiltration, such as in our case.\textsuperscript{3,4} In fact, the differential diagnosis for ring infiltrate is quite broad, and includes herpes simple keratitis, Gram-negative bacterial keratitis, fungal keratitis, and mycobacterial keratitis.\textsuperscript{3,4} Persistent epithelial defects can give an opportunity for superimposed infection, which can interfere with diagnosis and increase the difficulty of treating toxic keratitis. Smears and cultures of acanthamoeba and other pathogens should be obtained to rule out any possible superinfection. Delayed diagnosis of toxic anesthetic keratitis can result in corneal perforation and severe loss of vision.\textsuperscript{4}

Several mechanisms involved in the pathogenesis of keratopathy and the adverse effects of topical anesthetics have been proposed.\textsuperscript{1–5} Topical anesthetics can cause unstable tear film by decreased aqueous reflex tear production and diminished mucous adherence because of disruption of the microvilli of epithelial cells. Tear film instability, decreased reflex tearing, and a reduced blink rate combine to cause an increased rate of tear evaporation, which leads to more dryness and epithelial damage. Anesthetic interferes with epithelial metabolism by impairing the trophic function of the corneal nerve fibers. This results in intolerable pain of the insensitive cornea, which can force the patient to apply the anesthetic more frequently and cause a vicious cycle.

Topical anesthetic can cause punctate epithelial keratopathy and affect cell migration and division. The delayed epithelial wound healing and persistent epithelial defects are noted in epithelial toxicity.\textsuperscript{3} Proparacaine inhibits corneal epithelial migration and adhesion through alteration of the actin cytoskeleton. Dissociation of vinculin-based epithelial cell motility complexes can cause the release of another factor that can serve as an antigen.\textsuperscript{4,5} Immune recognition of this antigen might be responsible for the ring infiltrate. When epithelium is absent, the toxic effect of anesthetic can be enhanced markedly by direct exposure to the keratocytes of the corneal stroma. The toxic effects of direct exposure to the keratocytes include stromal infiltration, edema, and melting. Corneal stromal melting can cause corneal surface irregularity and haziness. Adverse effects of endothelial toxicity include endothelial pleomorphism, focal endothelial necrosis, cell loss, and numerous filamentous processes emanating from abnormally enlarged intracellular junctions.\textsuperscript{6} We believe that the major cause of endothelial cell loss in this patient was not so much related to her previous contact lenses wearing as to long-term abuse of dilute topical anesthetics. Direct toxic effects of or indirect immune reactions to topical anesthetics can also result in severe inflammation in the anterior chamber and keratic precipitates, which can cause further endothelial cell loss. In our case, more endothelial cell loss in the left than the right eye might have been caused by a different frequency of topical anesthetic abuse in both eyes, because of the presence of more keratic precipitates and stressed cells in the left eye.

Preservatives, such as 0.1% benzalkonium chloride (BAC) in proparacaine, are also toxic to corneal and conjunctival epithelium.\textsuperscript{7} The frequent application of medication that contains 0.004% BAC can cause severe endothelial damage.\textsuperscript{8} In addition to the long-term and frequent use of topical anesthetic in our case, the accumulative toxicity of BAC also could have contributed to corneal necrosis, thereby enhancing the toxicity of topical anesthetic.

Ethanol is used in the creation of the epithelial flap in LASEK surgery. Diluted ethanol induces an inflammatory response, corneal edema, and polymorphonuclear cell infiltration to the corneal stroma.\textsuperscript{9} Adverse effects of ethanol in keratocytes include breaking intercellular adhesion, apoptosis, and cell loss.\textsuperscript{30} MMC has been used to reduce
corneal haze and remove subepithelial fibrosis in photorefractive keratectomy or LASEK surgery but can cause corneal edema. The long-term use of topical MMC in pterygium surgery has been reported to cause severe ocular complications, including secondary glaucoma, corneal edema, corneal perforation, and iritis. In a rabbit model, delayed epithelialization, corneal edema, decreased endothelial density, and increased endothelial apoptosis have been observed upon application of 0.02% MMC for 2 minutes. MMC induces apoptosis in keratocytes and has latent effects within the intracellular or extracellular environment. Co-treatment with ethanol and MMC has shown synergistic damage in cultured corneal fibroblasts. In our case, diluted ethanol and 0.02% MMC for 2 minutes in LASEK surgery could have worsened anesthetic toxic keratopathy as a result of these adverse effects in corneal keratocytes and endothelial cells.

Serum contains epidermal growth factor (EGF), acidic and basic fibroblast growth factor (aFGF and bFGF), transforming growth factor (TGF) β, fibronectin, vitamin A, antiprotease, and neural factors. Autologous serum can accelerate the migration of corneal epithelial cells and help healing of corneal epithelial defects. EGF is present in tears and serum and has antiapoptotic properties. Additionally, EGF, aFGF, bFGF and fibronectin have been found to facilitate epithelialization. Serum antiprotease such as α2 macroglobulin inhibits corneal collagenase and decreases corneal melting. These beneficial effects of autologous serum might have contributed to rapid epithelialization and less corneal melting in our case. Autologous serum also harbors several neurotrophic factors, such as nerve growth factor, substance P, and insulin-like growth factor, and has been used to treat neurotrophic keratopathy. These neural factors induce neurite sprouting by neural cells and restore the function of injured neurons, therefore, autologous serum also can help regeneration of neurotrophic keratopathy caused by toxic anesthetic abuse.

Once the abuse of topical anesthetics has been diagnosed, the management of such a patient is cessation of use of the offending agent. In all cases, topical treatment of the vulnerable cornea should be kept to a minimum. Most cases with minor manifestations will resolve rapidly. Depending on the severity of the epithelial defect, preservative-free lubricants, patching, therapeutic contact lenses, collagen shields, and tarsorrhaphy have been suggested to facilitate healing of the epithelial defects and arrest destruction of the stroma. Severe or persistent corneal melting might require a conjunctival flap or amniotic membrane graft. In some instances, penetrating keratoplasty could be required to save vision, such as in cases with risk of corneal perforation or severe vision loss caused by corneal scarring and opacity. Most reported cases of toxic anesthetic keratitis with initially poor vision have been reported to have a long and poor visual recovery from no light perception to 20/80. Some cases have required penetrating keratoplasty to restore vision. In rare instances, enucleation has been carried out in patients with no visual potential. Chen et al reported that topical abuse of even a dilute anesthetic, 0.05% oxybuprocaine, could cause severe toxic keratitis, which led to poor vision. The good visual recovery in our case of severe toxic keratitis could have been because of early cessation of anesthetic and adjuvant application of autologous serum, although we did not perform a comparative treatment in each eye.

The physician must be aware of the signs of topical anesthetic abuse and consider it in the differential diagnosis of patients with chronic recalcitrant keratitis, especially with corneal ring infiltrates. Long-term topical abuse of dilute anesthetic can still cause severe toxic keratitis and permanent endothelial cell loss. Cytotoxicity of ethanol and MMC can exacerbate anesthetic toxic keratitis and should be taken into consideration in their use for refractive surgery. Conclusively, early diagnosis of toxic keratitis and discontinuation of the anesthetic agent is a key factor for saving vision. Autologous serum may accelerate reepithelialization of persistent epithelial defects and regeneration of neurotroph, and decrease corneal scarring formation in toxic.
keratitis. The temptation for anesthetic abuse is great; therefore, we recommend that the prescription of even a dilute topical anesthetic should be very cautious, and it should not be allowed for long-term usage.

References