EYE DROPS PRESERVATIVE AS THE CAUSE OF CORNEAL BAND KERATOPATHY IN LONG-TERM PILOCARPINE HYDROCHLORIDE TREATMENT

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SUMMARY – The aim is to present a patient with severe bilateral corneal complications after long-term antiglaucoma treatment with 1% pilocarpine hydrochloride (Pilokarpin, Pliva, Zagreb, Croatia) and its management. A patient with narrow-angle glaucoma treated with 1% topical pilocarpine hydrochloride eye drops for the last twenty years complained of impaired vision, intermittent visual haloes and eye redness. Ophthalmologic examination showed bilateral band keratopathy, peripheral laser iridotomy, medicamentous myosis, brown nuclear cataract, and synchysis scintillans of his right eye. Band keratopathy was thought to have resulted from the presence of the preservative phenylmercuric nitrate in the pilocarpine hydrochloride eye drops. Treatment of the patient consisted of two separate procedures for both eyes, i.e. phaco trabeculectomy and six months later corneal procedure including abrasion of corneal epithelium followed by removal of the superficial stromal calcium deposits by means of a 3.75% ethylenediaminetetraacetic (EDTA) solution. After phaco trabeculectomy, visual acuity was 0.8 on both eyes. Bilateral visual improvement with visual acuity 1.0 was recorded after corneal treatment with EDTA. In conclusion, one must be aware of preservative complications in long-term topical use, such as band keratopathy that can be visually incapacitating. Surgical treatment using EDTA is safe and effective treatment for band keratopathy.

Key words: *Pilocarpine hydrochloride; Band keratopathy; EDTA; Eye drops preservatives*

Introduction

Band keratopathy is a corneal degenerative disease associated with a variety of different ocular and systemic pathologic conditions. Its name derives from the distinctive appearance of calcium deposits in a band across the central interpalpebral corneal area. It is thought to result from precipitation of calcium salts on the corneal surface under the epithelium. Calcium salts can normally be found in serum or normal body fluids such as tears and humor aqueous. Central intrapalpebral corneal area shows greatest evaporations of tears tending to concentrate solutes. Systemic conditions with elevated serum calcium or serum phosphate can favor precipitation. Local conditions such as chronically inflamed eyes cause elevation of the eye surface pH that also favors precipitation.

Eye preservative complications have been described and reported[1-3] many times since their first use, while playing no significant role in short-term treatment. Glaucoma patients present a specific long-term treatment group with topical treatment that lasts for decades. Such length of treatment is the reason for the high incidence of preservative complications[4-6].

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Pilocarpine as an antiglaucoma medication is not frequently used today, although it is necessary in some specific cases. The exact incidence of calcium band keratopathy is unknown.

Surgical treatment of band keratopathy usually consists of removal of the corneal epithelium followed by removal of the subepithelial calcium deposits by means of ethylenediaminetetraacetic acid (EDTA) solution. EDTA has been used in such conditions for chelation of calcium ions. Chelator is not a solvent and does not dissolve anything. It is safe and effective treatment for calcium corneal deposits, although it is used 'off label'.

In order to reduce discomfort and postoperative pain that occurs after corneal abrasion, several modified methods have been developed using amniotic membrane[7], laser epithelial keratomileusis (LASEK)[8], bandage soft contact lens and phototherapeutic keratectomy[9], or their combination.

Case Report

A 65-year-old male patient was referred to the hospital for antiglaucoma surgery. He had a history of narrow angle glaucoma for the last twenty years. Nd:Yag laser iridotomy was done years before on both eyes, followed by treatment with topical 1% pilocarpine hydrochloride (Pilokarpin, Pliva, Zagreb, Croatia) eye drops three times daily ever since. In the last 12 months, he was complaining of impaired vision and intermittent visual haloes and occasional eye redness.

Ophthalmologic examination showed his best-corrected visual acuity (BCVA) of 0.075 on both eyes. Slit lamp examination revealed bilateral corneal band calcium deposits located in the subepithelial layer, laser peripheral iridotomies at 12 hours, medicamentous miosis, corticonuclear bilateral dark-brown cataract, and synchysis scintillans on his right eye.

The patient had no history of any systemic disease and was not taking any medications except for antiglaucoma eye drops. He had no family history of corneal disease and no history of trauma, arthropathy or inflammatory eye disease.

Thorough systemic evaluation did not reveal any abnormality. Routine hemogram was unremarkable. Serum levels of calcium and phosphorus, alkaline phosphatase, glucose, urea nitrogen and uric acid were normal. Since we did not find any local or systemic disease as the cause of the patient's band keratopathy, we considered it to have resulted from the presence of the preservative phenylmercuric nitrate in the pilocarpine hydrochloride eye drops.

Methods

Since our patient had multiple ocular pathologies, we decided to divide his treatment into two separate procedures for both eyes, as we could not establish how much the corneal deposits influenced his loss of vision. In the first procedure, mitomycin C enhanced fornix based trabeculectomy combined with phacoemulsification and intraocular acrylic lens implantation through a single incision was performed on the right eye and then on the left eye. Antiglaucoma eye drops were excluded after the first procedure.

Since visual axis was not clear six months after the first procedure, surgical corneal procedure in topical anesthesia including abrasion of corneal epithelium followed by removal of the superficial stromal calcium deposits by means of a 3.75% EDTA solution was performed. Cellular sponge soaked in the 3.75% EDTA solution was applied onto corneal deposits and kept for about 10 minutes, scraping several times avoiding central corneal zone. After white calcific deposits were dissolved, corneal surface was well irrigated with saline, bandage soft contact lens was placed and antibiotic eye drops were prescribed for seven days.

Results

After mitomycin C enhanced trabeculectomy combined with phacoemulsification and intraocular acrylic lens implantation, antiglaucoma topical therapy was excluded. At one month of the first procedure, BCVA was 0.8 on both eyes. Slit lamp examination showed conjunctival diffuse filtration bleb, band of calcific deposits and pseudophakia. Fundus examination showed no pathology. Intraocular pressure was 8-12 mm Hg.

Second procedure consisted of surgical corneal procedure including abrasion of corneal epithelium followed by removal of the superficial stromal calcium deposits with 3.75% EDTA solution. Follow up af-

ter second procedure was done at days 7, 14, 30 and 90, then at 12 and 24 months. Fourteen days after the second procedure, BCVA was 1.0 on both eyes. Removing corneal calcific deposits improved BCVA by two lines on Snellen charts. Intraocular pressure was 8-12 mm Hg. At 24-month follow up, BCVA and intraocular pressure were not changed. Slit lamp examination showed no recurrence or any other complication. Corneal surface stayed clear and smooth. The patient experienced no haloes or any other visual disturbances.

Discussion

Band keratopathy is a chronic degenerative condition commonly seen in association with a variety of other ocular and systemic conditions such as uveitis, absolute glaucoma, phthisis, chronic corneal edema, silicon oil and viscoelastic agents, steroid phosphate preparations, hypercalcemia and chemical burns. The condition can also be familial and idiopathic.

We found none of these causes to be responsible for corneal deposits in our patient.

In 1966, Charney reported a case described as idiopathic band keratopathy with no other ocular or systemic findings, and treated for eight years with miotics for glaucoma[10]. Five years later, Kennedy *et al*. reported atypical band keratopathy in 18 glaucoma patients on long-term miotic therapy[11]. It was then concluded for the first time that all affected individuals used pilocarpine made by one manufacturer, which differed from other brands available by containing phenylmercuric nitrate as a preservative agent. Since then, phenylmercuric nitrate has no longer been used in pilocarpine drops in western countries, but has still been present in some drops prescribed for glaucoma and antibiotic preparations.

In 1986, Douglas *et al*. reported similar corneal changes during pilocarpine gel therapy[12]. The exact mechanism of such corneal calcific deposits has not yet been precisely explained nor is the exact incidence of calcium band keratopathy known.

By pathological findings, band keratopathy is divided into two different subtypes according to the impacted layer, i.e. superficial type and deep type. It is also divided into three stages according to symptoms and disruption of the ocular surface. Our patient had superficial type medium stage band keratopathy, which can be considered as the reason for good result and fast recovery leaving no postoperative corneal haze. EDTA applied for about 10 minutes dissolved calcific deposits in the central corneal area because they were superficial and not too thick. We did few gentle peripheral corneal zone scrapings near limbus using blunt spatula outside the visual axis to remove thicker deposits. If deposits were much thicker, then EDTA can be instilled for much longer until calcium plague is dissolved completely. Deep corneal stromal deposits leaving defect could potentially delay healing and would ask for another approach like superficial lamellar keratectomy, phototherapeutic keratectomy, LASEK, amniotic membrane transplantation, and their combination.

It is also known that exposure to mercury vapor causes brown discoloration of the anterior lens capsule[13], so called mercurialentis. The same effect is exerted with phenylmercuric nitrate as preservative. Such dark-brown colored cataract was the cataract that our patient had on his both eyes.

At 24-month follow up, our patient had no recurrence, although Najjar *et al*. report a high incidence of late recurrence, with a case of recurrence even after 17 years[14]. However, early and high recurrence rate is expected in rare familial calcific band keratopathy[15]. Since our patient has no family history, no systemic related diseases, and has been left without any topical medications, we presume he has a very little chance of recurrence. However, treatment with EDTA is repeatable.

Commercial ophthalmic preparation for chelation such as EDTA is not available yet. EDTA is available as 100% solution that can easily be diluted with saline. Treatment with EDTA chelation proved to be surgically easy and safe procedure.

Conclusion

Phenylmercuric nitrate is still used as a preservative in some topical medications. In glaucoma patients, their long-term use can cause side effects that can lead to visual impairment. Treatment of band keratopathy depends on its stage and subtype. EDTA as a chelation agent for corneal calcific plaque is a safe and effective method for its complete removal. The

procedure is simple and the results are excellent, with good recovery of vision.

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Sažetak

KONZERVANS U OČNIM KAPIMA KAO UZROK POJASASTE KERATOPAIJE ROŽNICE KOD DUGOTRAJNE TERAPIJE PILOKARPIN HIDROKLORIDOM

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Cilj je prikazati slučaj nastanka rožničnih komplikacija uzrokovanih konzervansima pri dugotrajnoj upotrebi kapi 1%-tnog pilokarpin hidroklorida (Pilokarpin, Pliva, Zagreb, Hrvatska) i njihovo liječenje. Bolesnik s glaukomom zatvorenog kuta koji se unazad dvadeset godina liječio antiglaukomskim kapima 1%-tnog pilokarpin hidroklorida tri puta na dan žalio se na slabiji vid, haloe i povremeno crvenilo očiju. Oftalmološkim pregledom nađene su obostrane pojasaste degeneracije rožnice, periferne laserske iriditomije, zjenice u medikamentnoj miozi, tamna nuklearna bilateralna katarakta i scintilirajuća sinhiza desnog oka. Konzervans živin nitrat smatra se uzrokom pojasaste degeneracije rožnice kod ovoga bolesnika. Liječenje bolesnika sastojalo se od dva postupka za oba oka: prvi je bio kombinirani zahvat fakoemulzifikacije katarakte s trabekulektomijom, a nakon šest mjeseci liječenje koje je uključivalo abraziju kornealnog epitela i uklanjanje stromalnih kalcijskih depozita pomoću 3,75%-tne otopine etilendiamintetraoctene kiseline (EDTA). Vidna oštrina nakon fakotrabekulektomije bila je 0,8 na oba oka. Obostrano poboljšanje vida do vidne oštrine 1,0 postiglo se nakon uklanjanja rožničnih depozita pomoću EDTA. Zaključuje se kako se prilikom dugotrajne upotrebe lijekova s konzervansima mogu očekivati nuspojave kao što je pojasasta degeneracija rožnice koja može doprinijeti znatnom smanjenju vidne oštrine. Kirurško liječenje pomoću EDTA je sigurna i učinkovita metoda liječenja pojasaste degeneracije rožnice.

Ključne riječi: *Pilokarpin hidroklorid; Pojasasta degeneracija; EDTA; Konzervansi u topikalnoj terapiji*