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MODERN APPROACH IN THE TREATMENT OF RECURRENT CORNEAL EROSION

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SUMMARY - Recurrent corneal erosions, independently of the origin, seem to show a similar tendency to abnormal adhesion between corneal epithelium and stroma. Although, for general ophthalmologist, it may at first seem to be one of the less difficult entities to diagnose and therefore to treat, for a patient suffering from this disorder it may be very frustrating, and sometimes even frightening. The majority of patients will respond to simple measures such as padding and antibiotic ointment, but there are a percentage of patients that require a more complex approach. The common goal of each conservative or surgical treatment is fast healing and encouraging proper formation of adhesion complexes between the epithelium and the stroma, without any infections or recurrences. The objective of this review is to assess the indications and outcomes of current treatment options for recurrent corneal erosion, based on literature survey. Briefly, in spite of the many different treatment options, there is still room for further research in the area. Phototherapeutic keratectomy opens a new line of possibilities and it should be considered as very effective therapy for refractive cases. Also, in spite of our recommendations, each patient should be treated individually.

Key words: cornea, phototherapeutic keratectomy, recurrent corneal erosion

Background

The cornea is a transparent avascular tissue that serves the eye in two ways. First, it provides a physical barrier that shields the inside of the eye from any harmful matter such as infection or structural damage, and shares this protective task with the sclera. Second, it acts as the eye's outermost lens and is necessary to provide a proper anterior refractive surface. The tear-air interface, together with the underlying cornea, provides roughly two thirds of the total refractive power of the eye.

The tissue is arranged in five main layers but when discussing recurrent corneal erosion, epithelium is the layer to focus on. It consists of three types of cells: polygonal, suprabasal (wing) and basal cells. Polygonal cells play an important role in increasing the surface area of the contact between tear film and cell membrane. The barrier tight-junctional complexes on their lateral sides restrict entry of the tears or dyes into the intercellular spaces. Suprabasal cells beneath have similar tight junctions. Single-cell layer of basal cells is the only one capable of mitosis and responsible, together with epithelial stem cells localized to the limbal basal epithelium, for epithelial regeneration. They also secrete extracellular matrix which makes basement membrane. The epithelial bond to the underlying basement membrane, after its destruction, tends to be unstable during the healing period of 6 weeks. This period is needed for the reconstruction of basement membrane. These facts are important when dealing with recurrent corneal erosion.

Complete turnover of corneal epithelial cells occurs in about 7-10 days[1]. Epithelial regeneration happens according to the "X, Y, Z hypothesis"[2]. These phenomena are co-dependent and controlled by feedback mechanism depending on the cell distribution and cell layer thickness.

After the injury, cells at its edge begin to cover the defect as rapidly as possible by a combination of cell

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migration and cell spreading. Depending on the size of the injury, this process begins immediately after minor defects and within 4-5 hours after major defect. This early nonmitotic phase of wound coverage is remarkable for its speed which is 60-80 μm/h[3]. Mitosis and cell proliferation begin 24-30 hours after medium sized injury, and are prolonged to up to 96 hours when the defect is large[4]. So, the epithelial healing process begins when basal epithelial cells undergo mitosis, producing new cells that occupy fresh wounds. Any disruption to basal cell production will make the eye more prone to recurrent erosion.

Various conditions may delay normal healing process such as damage to the cellular substrate caused by infectious disease, diabetes, chemical burns, dystrophies, ocular surface inflammation, dry eyes, neurotrophic or exposure keratopathies, conjunctival disease, extensive damage to the limbal stem cells, eyelid abnormalities, etc. The underlying condition is then treated.

If there is no such condition present, most of the defects heal quickly and permanently. Even so, some may show recurrent breakdowns of epithelium, sometimes several years after the initial episode, and cause recurrent corneal erosion syndrome.

The primary clinical etiology of recurrent corneal erosions includes epithelial dystrophies (map dot fingerprint dystrophy, also known as epithelial basement membrane dystrophy or Cogan microcystic dystrophy), Meesmann's dystrophy (hereditary juvenile epithelial dystrophy), Bowman's membrane dystrophy (Reis-Bücklers I and II), and stromal dystrophies (macular, lattice, or granular dystrophies). Approximately half of the patients with recurrent corneal erosions have map-dot fingerprint dystrophy, while 10% of patients with anterior basement dystrophy have recurrent corneal erosions.

Secondary clinical etiologies include mechanical trauma (fingernails, paper), surgery, and miscellaneous disorders (diabetes, dermatological diseases). Posttraumatic, nondystrophic recurrent corneal erosion is clinically the most common form. After corneal surface injury, basement membrane thickening, discontinuities and duplications are seen for 8-12 weeks, so the overlying epithelium is vulnerable to detachment during this period[5-7]. It is well known that injuries associated with carbon-based moieties such as a child's fingernail or a paper cut will more likely lead to recurrent erosions than a metallic injury. This relates to the disturbance of the stereochemistry of the anchoring fibrils and the basement membrane of the basal epithelial cells.

Those of primary clinical etiology usually produce a microform, and those after trauma a macroform of the disorder[8].

Refractive surgery including LASIK and PRK can induce or precipitate symptoms of recurrent corneal erosions[9,10]. Surgeons must minimize epithelial damage to prevent recurrent corneal erosions after LASIK. According to Ti and Tan, adequate irrigation of the corneal surface immediately before microkeratome pass and careful attention to flap epithelium during flap replacement reduce epithelial damage[9].

Patients with recurrent cornel erosion usually present with a history of corneal abrasion in the involved eye, often months or years before, and the main complaint of recurrent episodes of ocular pain that may also include foreign body sensation, photophobia, blepharospasm, decreased vision or lacrimation upon awakening or following eye rubbing or eye opening.

Clinical signs include a localized, visible roughening of the corneal epithelium which stains superficially with fluorescein dye. The lesions are typically unilateral and in the vicinity of the original corneal defect. Bilateral or idiopathic lesions suggest a basement membrane dystrophy. The phenomenon may occur as frequently as daily or as sparsely as biweekly or monthly, even yearly.

Epithelial basement dystrophy is an associated finding in many cases. It is marked by small, intraepithelial dots and subepithelial ridges and lines ("maps", "fingerprints"), representing poor adhesion of the epithelial basement membrane and Bowman's layer. Retroillumination is diagnostically important.

Current Practical Considerations

The common goal of each conservative or surgical treatment is fast healing and encouraging proper formation of adhesion complexes between the epithelium and the stroma without any infections or recurrences.

At the time of the episode, the treatment consists of *cycloplegia* (atropine 1% for severe cases, homatropine 5% for moderate cases, and cyclopentolate 1% for mild cases) and a *topical antibiotic* such as tobramycin (Tobrex). Also, inactivity and analgesics are recommended. If the pain is severe, then *topical nonsteroidal anti-inflammatory drops* can be prescribed. Today, *pressure patching* is somewhat controversial. *Bandage soft contact lenses* have nearly supplanted the traditional pressure patch in the management of corneal abrasions. Extended wear bandage

soft contact lenses may provide comfort and support the healing process, with minimal compromise of vision. They should remain on the cornea for at least 6-8 weeks. If a contact lens is used, then the lens should be fit tight and the physician and the patient should be aware of the risk of microbial keratitis.

After the episode has subsided, *lubrication* such as artificial tears and artificial tear ointment may be applied to prevent mechanical epithelial trauma from the eyelids. Ocular lubricants are the standard treatment for recurrent corneal erosion. Loose flaps of epithelium should be removed before prescribing lubricants. In some dystrophic cases, reduplicated basement membrane can be scraped off before lubricant treatment is resumed. Loose corneal epithelium that impedes healing should be debrided. Lubrication should be continued for 3 to 6 months after erosion.

Hypertonic saline (5% sodium chloride) drops or ointment may be applied if the patient has a recurrence while using artificial tears and ointment. Hypertonic agents may transiently produce an osmotic gradient, drawing fluid from the epithelium, and may promote the adherence of epithelial cells to the underlying tissue. Brown and Bron[8] have reported benefit from using long-term topical 5% NaCl ointment (for 18 months) for clinical improvement in patients with recurrent erosions.

The activity of gelatinase (MMP-2 and MMP-9) is up-regulated in corneal epithelial specimens of patients with recurrent corneal erosions[11-13]. During wound healing, the epithelial basement membrane is altered by gelatinases, which cleave collagen types IV, V, VII and X.[11-13] Immunolocalization studies suggest that MMP-2 (gelatinase) is concentrated in basal epithelial cells where it may play an important role in degradation of the epithelial anchoring system and the recurrent epithelial slippage and erosion observed in patients[11]. Medications that *inhibit metalloproteinase-9* produce rapid resolution and prevent further recurrence of recalcitrant recurrent corneal erosions[11,14]. Dursun et al. suggest that recalcitrant recurrent corneal erosion can also be treated with inhibitors of matrix metalloproteinase-9 such as tetracycline (250 mg twice a day for 12 weeks)[12].

Some novel treatments which are still under observation are opioid antagonists such as naltrexone[15-18], CFTR activators[19,20], topical fibronectin eyedrops21, topical tretinoin-a vitamin A analog[22,23], growth factors, and autologous serum eye drops[24]. These agents influence epithelial migration, mitosis, apoptosis, adhesion and differentiation in various ways, and are studied as possible therapeutic agents which enhance corneal epithelial healing.

All of the above represent conservative approach, except for the mentioned debridement. It represents the simplest surgical approach by scraping of loose epithelium of the affected area with cellulose spear, a smooth-edged nonincisional instrument such as Kimura spatula, or by lifting it with fine surgical forceps. Sharp instruments should be avoided. While performing it, the surrounding area should also be checked with a cellulose spear for the presence of loosely adherent epithelial sheets. Alcohol delamination or debridement of the corneal epithelium is also an option which is still under research[25,26].

The next, more aggressive option is *anterior stromal micropuncture*. It was first described by McLean et al.[27]. The ophthalmologist uses a 25-gauge needle to make superficial puncture wounds in the involved area. These wounds produce a firm adhesion between the epithelium and the underlying stroma, where epithelial plugs work as an anchors in the puncture sites. It is preferred to leave the central optical zone clear.

The same effect can be achieved by use of *argon or YAG laser, surface cauterization or diathermy*. Judge et al. suggest that it does not show any advantages over the needle because of more scarring and corneal topographic changes[28].

The last surgical option is *superficial keratectomy*. It can be done *mechanically* or by laser. It removes the diseased basement membrane down to the Bowman's layer and superficial stroma. This method cleans Bowman's membrane resulting in a fresh substrate onto which the epithelium can regrow and create attachment complexes.

A scarifier blade or blunt lamellar dissection blade can be used to peel and dissect off changed tissue. Also, fine grade diamond polishing drill is used to remove ill tissue and polish the surface of the cornea. Soong et al. compared it with dissectional methods and found it less technically demanding while achieving better results[29].

Excimer laser photo-therapeutic keratectomy (PTK) is now a well-established treatment modality for recurrent corneal erosion and is being used both safely and effectively. Partial ablation of Bowman's layer with PTK gives a smooth surface for the newly generating epithelium to migrate and form adhesion complexes. A modulating agent such as methylcellulose is used to coat the depressions and expose the peaks in the cornea for the

laser to work on. This technique permits precise removal of adherent abnormal basement membrane and allows the new epithelium to adhere to the fresh substrate. The minimal ablation depth usually results in an insignificant refractive shift. There are several different PTK techniques. Subepithelial technique (conventional) first includes debridement of the epithelium and then the laser energy is emitted onto the involved area. Transepithelial technique does not involve removal of the epithelium. The laser works directly onto the corneal surface. Aggressive PTK is a technique where the ablation goes to deeper layers up to 20-μm depth. In comparison to other forms of PTK, aggressive PTK showed the lowest recurrence rate as reported by Eschstruth and Sekundo for a long-term follow-up[30]. Intraoperative application of mitomycin C after PTK shows, according to Haschemi et al., reduction of recurrences and haze[31].

Conclusion

The choice of treatment may be affected by the etiology, location of disease (axial or off-axis), coexisting ocular diseases, individual patient reliability, availability of equipment and evaluation of corneal topography, including the surface regularity index (SRI) and surface asymmetry index (SAI).

If the etiology and location of the involved area is our leading factor for the choice of therapy, then the first step is to divide them into two groups, dystrophic or primary and posttraumatic or secondary group[32]. Primary cases are usually refractive to conventional therapy; so Eschstruth and Sekundo30 and Starr et al.[33] recommend PTK. Diamond burr or debridement are desirable methods according to Soong et al.29 and Sridhar et al.[34]. Secondary cases respond to conventional therapy combined with contact lenses, and they are the methods of choice when dealing with changes near the axial location[35-37], but anterior stromal micropuncture is the way to go when dealing with paraxial changes[27, 28].

The severity of clinical symptoms is another factor which helps us choose the best treatment for recurrent corneal erosion. If the symptoms are mild, conventional therapy should cover the problem. More extensive symptoms will lead us to the use of debridement or soft contact lens, and severe and frequent symptoms leave us with anterior stromal micropuncture or superficial keratectomy, mechanical or laser, as therapeutic options. Many authors agree that PTK has long lasting effects, better visual outcome, less recurrence, and should be our first choice when treating these cases refractory to conventional therapy[30,33,38-42].

On evaluation of corneal topography, evidence of an irregular topography suggests corneal scraping, so that the epithelium has a chance to grow back and smooth out the surface. Significant improvement in topography and vision may be seen after epithelial scraping. Evidence of a regular topography according to Donnenfeld et al. would be an indication for anterior stromal puncture rather than corneal scraping[43].

Individual patient reliability is something every physician should evaluate for himself, depending on the atient's social status, intelligence and motivation.

In the end, we can say that in spite of many different treatment options, there is still room for further research in the area.[11-19,30-33,35]. However, PTK opens a new line of possibilities and it should be considered as very effective therapy for refractive cases. Our recommendations are a product of clinical experience and reviewed literature. They are only suggestions and repetition of our knowledge so far. Although, for general ophthalmologist, it may at first seem that recurrent corneal erosion is one of the less difficult entities to diagnose and therefore to treat, for the patient suffering from this disorder it can be very frustrating and sometimes even frightening. In spite of this article, every patient should be approached, diagnosed and treated individually and with due consideration of all mentioned above.

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Sažetak

SUVREMENT PRISTUP U LIJEČENJU RECIDIVIRAJUĆE EROZIJE ROŽNICE

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Recidivirajuće erozije rožnice, neovisno o uzroku, pokazuju sličnu tendenciju abnormalnoj adheziji između rožničnog epitela i strome. Iako za općeg oftalmologa dijagnosticiranje ovoga poremećaja, a time i liječenje predstavlja jedno od lakših entiteta, bolesniku ovo stanje može biti vrlo frustrirajuće, a ponekad i zastrašujuće. Većina bolesnika pozitivno reagira na jednostavne mjere kao što su zatvaranje oka zavojem i antibiotske masti, no postoji i dio bolesnika koji zahtijevaju složeniji pristup. Zajednički cilj svakog konzervativnog ili kirurškog liječenja je brzo cijeljenje i poticanje pravilnog formiranja adhezijskih kompleksa između epitela i strome bez infekcije ili recidiva. U ovom osvrtu je cilj predstaviti indikacije i rezultate današnjih opcija liječenja vezanih uz recidivirajuće erozije rožnice zasnovanih na istraženoj literaturi. U zaključku, možemo reći kako usprkos mnogim različitim opcijama liječenja još uvijek ima mjesta za daljnja istraživanja na ovom području. Fototerapijska keratektomija otvara nove mogućnosti i trebala bi se uzeti u obzir kao vrlo uspješna terapija refraktornih sučajeva. Također, usprkos našim preporukama, svakog bi se bolesnika trebalo liječiti individualnim pristupom.

Ključne riječi: rožnica, fototerapijska keratektomija, recidivirajuća erozija rožnice