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REVIEW

Corneal Regeneration After Photorefractive Keratectomy: A Review☆

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Abstract Photorefractive keratectomy (PRK) remodels corneal stroma to compensate refractive errors. The removal of epithelium and the ablation of stroma provoke the disruption of corneal nerves and a release of several peptides from tears, epithelium, stroma and nerves. A myriad of cytokines, growth factors, and matrix metalloproteases participate in the process of corneal wound healing. Their balance will determine if reepithelization and stromal remodeling are appropriate. The final aim is to achieve corneal transparency for restoring corneal function, and a proper visual quality. Therefore, wound-healing response is critical for a successful refractive surgery. Our goal is to provide an overview into how corneal wounding develops following PRK. We will also review the influence of intraoperative application of mitomycin C, bandage contact lenses, anti-inflammatory and other drugs in preventing corneal haze and post-PRK pain.

PALABRAS CLAVE
Queratectomía fotorrefractiva;
Córnea;
Curación de heridas;
Lentes de contacto

Regeneración de la córnea tras queratectomía fotorreactiva: revisión bibliográfica

Resumen La queratectomía fotorrefractiva (PRK) remodela el estroma de la córnea para compensar los errores refractivos. La eliminación del epitelio y la ablación del estroma provoca la alteración de los nervios corneales y la liberación de diversos péptidos de la lágrima, epitelio, estroma y nervios. Innumerables citoquinas, factores de crecimiento y metaloproteasas de la matriz participan en el proceso de regeneración y cicatrización corneal. Su equilibrio determinará si la re-epitelización y la remodelación del estroma son adecuados. El objetivo final

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es el logro de la transparencia corneal para restablecer la función de la córnea, así como la calidad visual adecuada. Por tanto, la respuesta de regeneración y cicatrización corneal es esencial para el éxito de la cirugía refractiva. Nuestro objetivo es aportar una visión general sobre el modo en que se desarrolla dicho proceso tras la PRK. Revisaremos también la influencia de la aplicación intraoperatoria de mitomicina C, lentes de contacto terapéuticas, y otros fármacos para prevenir el haze y el dolor tras la PRK.

The ablation surgery of the corneal surface for the correction of refractive errors began with the development of the excimer laser. The acronym laser means ''Light Amplification by the Stimulated Emission of Radiation''. Photorefractive keratectomy (PRK), developed by Trokel and colleagues in 1983, uses an excimer laser that emits ultraviolet light of 193 nanometers (nm), a combination of Argon and Fluor (ArF) to remodel the corneal.[1–6] It was not until 1996 when the Food and Drug Administration (FDA) aproved PRK as a refractive surgery technique.[7] In PRK the excimer laser acts on the anterior corneal stroma,[2,8,9] producing a stromal remodeling, and, consequently, inducing a change in corneal refraction.[10,11] It corrects mild to moderate myopia, hyperopia and astigmatism, with high level of safety and efficacy.[3,11–20] However, the use of PRK has been reduced over the past years by the introduction of the Laser In Situ Keratomileusis (LASIK).[12,21] Although LASIK provides less postoperative pain, less inflammation, and faster corneal wound healing and visual recovery,[8,17,19,22–25] PRK may be a useful alternative in post-radial keratotomy,[26–28] post-penetrating keratoplasty,[29] in thin corneas, irregular topographies, alterations of the basal membrane, treatment of some LASIK flap complications or residual refractive errors after LASIK.[11,12,19,30–32] It is also indicated in military pilots, professional athletes, or patients that have a high risk for traumatic postoperative flap dislocation.[12,31] In addition to the above-mentioned advantages, the PRK has gained popularity with the recent wave front guided laser ablation, which reduces postoperative high order aberrations (HOA), improving the optical quality.[30]

The visual quality might not be optimal if some complications take place, like subepithelial corneal haze, epithelial hypertrophy, regression of refractive error, deposition of subepithelial extracellular matrix or fibrosis. Other adverse effects include postoperative pain, abnormal corneal nerve regeneration, and night vision symptoms like halos and glare.[3,10,11,14,18,22,33–40]

The purpose of this review is to explain the main cellular changes and complications that occur in different corneal layers after PRK, and to explain how they affect the visual quality. We discuss the role of mytomicin C and bandage contact lenses in corneal regeneration, and the role of different drugs in postoperative corneal pain management.

Corneal Wound Healing

Corneal wound healing is a complex process that, in normal conditions, culminates in the restoration of the tissue, without scar formation or vascularization. The aim is to maintain transparency to recover a proper visual function. After epithelial injury, the corneal healing starts with the removal of necrotic cells.[41] Fibronectin provides a transient matrix for the adhesion of migrating cells, until an epithelial monolayer covers the injured area.[42] Fibronectin also stimulates the production of plasminogen activator (PAA), and by a cascade of events, cell-subepithelial matrix adhesions break down.[42] In the next step, limbal stem cells undergo mitosis to reestablish lost cells, and with the anchoring of hemidesmosomes to the underlying stroma, the epithelial regeneration process completes.[41] Stromal wound healing depends on epithelial cells, and on their interaction with keratocytes.[43] Following stromal injury, released cytokines induce the apoptosis of keratocytes under the wound, and stimulate the proliferation and migration of neighboring keratocytes.[44] These active keratocytes synthesize matrix metalloproteases (MMP) to remodel the stroma. At later stages, a number of them take the repair phenotype, the so-called myofibroblasts,[45] and produce collagen and extracellular matrix (ECM), until the basement membrane prevents the inflow of cytokines in the stroma, and myofibroblast, presumably, commit apoptosis (Fig. 1).[46,47]

Epithelial Wound Healing Following PRK

The corneal epithelium is formed by superficial, wing and basal cells.[48,49] In order to facilitate the stromal ablation in PRK, the corneal epithelium is removed. The absence of the epithelium will condition corneal repair. Corneal epithelial cells are the first cells involved in the corneal regeneration process after PRK.[50] Epithelial cells proliferate and migrate from the limbus and the basal epithelial layer to reestablish corneal layers.[8,51] Corneal regeneration after PRK can be better understood using current, non-invasive, confocal microscopy. It has been used on animals and on humans for corneal cellular structure visualization in real time.[2,5,10,22,25,40,48] Esquenazi et al.[22] proved using a new generation high-resolution in vivo confocal microscope that environmental conditions influenced the regeneration of the corneal epithelium. They showed that the number of the superficial cells was reduced in desiccating environments compared with normal conditions, and the number of basal epithelial cells was increased. Histological studies conducted in animals and in humans, have found that corneal epithelium is thicker after PRK,[2,52] caused by an elongation of the basal epithelial cells and an increased number of superficial cell layers.[25] The corneal flattening in myopic PRK may result in postoperative epithelial thickening due to