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Long-term results of corneal collagen crosslinking for recurrent corneal erosion

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BACKGROUND: Recurrent corneal erosion (RCE) is characterized by excacerbation and remission episodes, reduced patient's quality of life affecting their daily and professional activities. In case of conservative therapy inefficacy surgical procedures are used (Bowman's membrane polishing with diamond drill, excimer laser phototherapeutic keratectomy, anterior stromal puncture, and amniotic membrane transplantation). All methods have their advantages and weak points, as well as a certain percent of recurrence. In this regard the use of corneal collagen cross-linking is of the interest as an alternative method of the RCE surgical treatment.

MATERIALS AND METHODS: 18 patients (20 eyes) with RCE without central corneal stroma scars, aged from 30 to 66 (average 49,5 ± 10,6, all women), after conservative treatment failure (more than 6 months) underwent cross-linking according to the Dresden protocol with the UVX device, version 1000, by IROC INNOCROSS (Switzerland).

RESULTS: All patients were asymptomatic and had no recurrence during the observation period (from 1 to 6 years, in average 2,6 ± 1,6). There was a slight but statistically significant BCVA improvement (from 0,93 ± 0,09 at baseline to 0,97 ± 0,07 after intervention).

CONCLUSIONS: Crosslinking may be an additional and effective treatment in a number of RCE cases when there is no central corneal stromal scars present. To reduce stromal keratocytes alteration during the procedure modified protocols may be used.

Keywords: recurrent corneal erosion; corneal crosslinking; phototherapeutic keratectomy.

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Отдалённые результаты кросслинкинга роговичного коллагена при рецидивирующей эрозии роговицы

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Введение. Рецидивирующая эрозия роговицы (РЭР) характеризуется чередованием периодов обострений и ремиссий, существенно снижая качество жизни пациентов, затрудняя их бытовую и профессиональную деятельность. При неэффективности консервативной терапии прибегают к хирургическим методам лечения: шлифовке боуменовой мембраны алмазным бором, фототерапевтической кератэктомии, передней стромальной пункции, трансплантации амниотической мембраны. Каждый метод имеет свои преимущества и недостатки, а также определённый процент рецидивов. В этой связи в рамках поиска альтернативных методов хирургического лечения РЭР представляет интерес применение кросслинкинга роговичного коллагена (КРК).

Материалы и методы. 18 пациенткам с РЭР в возрасте от 30 до 66 лет (средний возраст 49,5 ± 10,6 года) на фоне неэффективности консервативного лечения (более 6 мес.) был выполнен КРК по Дрезденовскому протоколу на приборе UV X версии 1000 компании IROC INNOCROSS (Швейцария).

Результаты. У всех пациенток отмечено полное купирование симптомов РЭР и отсутствие рецидивов за период наблюдения (от 1 года до 6 лет, в среднем 2,6 ± 1,6 года). Было выявлено незначительное, но статистически значимое повышение максимальной корригированной остроты зрения (до КРК 0,93 ± 0,09 / после 0,97 ± 0,07).

Выводы. КРК может быть дополнительным и эффективным методом лечения РЭР в тех случаях, когда нет центральных стромальных помутнений. В дальнейшем целесообразно использовать методики модифицированного кросслинкинга, ограничивающие его воздействие по глубине, во избежание неблагоприятного эффекта на кератоциты стромы.

Ключевые слова: рецидивирующая эрозия роговицы; кросслинкинг; фототерапевтическая кератэктомия.

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INTRODUCTION

Recurrent corneal erosion (RCE) is a chronic disease of unknown etiology, manifested by spontaneous disruption of the integrity of the anterior corneal epithelium, corneal syndrome, and decreased vision.

Episodes of exacerbations reduce significantly the quality of life of the patients, complicating their everyday life and professional activities. RCE occurs in group aged 20–80 years, but people of working age (30–40 years old) experience it more often; therefore, it affects not only the social but also the professional sphere of the patients' activity due to forced interruptions in work.

A characteristic sign of RCE is desquamation of the corneal epithelium in some of its areas. RCE was first described by Hansen in 1872, calling it "intermittent neuralgic vesicular keratitis" [1]. Two years later, in 1874, Von Arlt published a similar standpoint, but called it "recurrent erosion" [2]. Further developments in ophthalmology contributed to a more detailed visualization of existing corneal changes in this condition. To date, insufficient adhesion of the basement membrane of the anterior corneal epithelium to Bowman's membrane in some of its parts due to the impaired functioning of the adhesive complex is considered as the RCE cause.

RCE most often occurs in the eyes with a history of trauma (45%–64%), dystrophy of the basal epithelial membrane (19%–29%), other dystrophies, and corneal degenerations (such as lattice dystrophy and band-shaped keratopathy) [1]. In addition, RCE occurs after various surgical interventions (refractive surgery of the cornea, keratoplasty, and cataract surgery). Factors that aggravate the disease course include dry eye syndrome (DES), diabetes mellitus, blepharitis, rosacea, and lagophthalmos (including nocturnal one), as well as eyesight strain, menopause, and alcohol intake [1, 3].

Several theories tried to explain the RCE development. Hansen and Von Arlt considered trauma of the corneal epithelium as the main etiological factor of RCE. Swedish scientists led by Hammar confirmed these data and discovered that corneal epithelium stratification occurred only at the site of previous injury. Even if a person is genetically predisposed to the development of RCE, erosion does not develop if the cornea has not been previously damaged. Hammar et al. [4] also described a special case of recurrent erosion (*Distrophia Smolandiensis*).

At the cellular level, RCE of traumatic origin is associated with poor regeneration of anchor fibers by hemidesmosomes [5, 6]. Hemidesmosomes located in the basal layer of corneal epithelial cells are part of the anchoring complex that provides a structural link between the intracellular cytoskeleton and the basement membrane of the epithelium, Bowman's membrane, and stroma [1]. Damage to the corneal epithelium triggers a whole cascade of reactions leading to changes in cell–cell interactions and inflammation, which, in turn, further destroys the epithelial basement membrane and weakens the adhesion, forming a vicious circle of the pathological process and slowing down the regeneration.

Unlike traumatic erosions, erosions of dystrophic origin arise from a malformation of the basement membrane–anterior corneal epithelium complex [4] – as in the case of dystrophy of the basement membrane of the anterior epithelium (in particular, Cogan dystrophy as one of the most common "anterior" dystrophies in the population, occurring in 5%–15% of the population) [1, 7]. Cells of the anterior corneal epithelium (from the basal layer to the surface layer), migrating during the natural life cycle, are trapped under additional layers and outgrowths of the basement membrane, which results in the disruption of their desquamation, accumulation of degradation products in the epithelial layer thickness, and disruption of its normal architectonics and adhesion [8]. An increase in the expression of matrix metalloproteinases (MMP-2 and MMP-9) in such areas of the cornea was noted, which jointly leads to the degradation of the extracellular matrix, deficiency of integrins, and destruction of the adhesion complex [1, 9].

Histological studies in patients with RCE demonstrate segmental absence of hemidesmosomes and basement membranes, intercellular edema, and decrease in the number of anchor fibers [10].

Valle et al. advocated the hereditary theory of RCE. Franceschetti (1928), Chandler (1945), and Wales (1955) have reported the dominant mode of inheritance of this disease. In 2010, Kucherenko et al. published data on the role of polymorphism of interleukin (IL-6 and IL-8) genes in the development of RCE [2, 11, 12].

Diagnosis of RCE

The diagnosis is made clinically based on complaints, past medical history, and biomicroscopy data with fluorescein test. In biomicroscopy, not only the defect of the epithelium and its edges required attention, but the state of the cornea beyond this zone should be assessed carefully, and the presence of intraepithelial microcysts, "geographical map," and "fingerprints" haze, including cicatricial haze after injuries or surgical interventions, should be ruled out. Intraepithelial corneal haze is clearly visible against a red reflex during retroillumination. According to Pronkin and Maychuk, the erosion is most common in the lower paracentral zone (68.4%) [2]. The patient should be necessarily asked about the presence of corneal dystrophies in relatives as well as about a history of corneal trauma. Erosion is often accompanied by meibomian gland dysfunction (MGD) and dry eye syndrome (DES), so these manifestations must be taken into account when choosing the treatment option.

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Patients with RCE usually experience sudden eye pain and frequent sleep awakening associated with corneal syndrome (i.e., redness, photophobia, pain, foreign body sensation, blurred vision, and lacrimation). The onset of symptoms in the morning after sleep is associated with several factors. First, this is the mechanical detachment of the loosely adhered anterior epithelium due to the sharp movement of the eyelids when they open during awakening or rapid movements of the eyeballs during desynchronized sleep. Second, it is a consequence of the tear film thinning at night, which contributes to a closer contact of the palpebral conjunctiva with the superficial epithelial layer of the cornea, with natural physiological edema of the latter. This explains the occurrence of erosion during the first opening of the eyelids in places where its attachment to the basement membrane is loose [13].

For better visualization of pathological changes in the epithelium, confocal microscopy of the cornea is used, which allows observation of epithelial microcysts and abnormalities of the epithelium basement membrane, areas of its cleavage, and penetration into the epithelial layer thickness, when they are still poorly visible during biomicroscopy [14].

Optical coherence tomography with epithelial mapping is used to measure the epithelial layer thickness of the cornea [1], which is important when monitoring a patient in time. With keratotopography, depending on the area of pathological changes in the corneal epithelium, areas of change in the optical power of the cornea with a diameter of ⩾1 mm and irregular astigmatism can be identified. Both of these examination methods are important when choosing surgical treatment for patients with RCE.

Conservative treatment of patients with RCE

Lowe, based on his own research, stated that the prevention of RCE relapse should be based on two key principles [14]: (1) prevention and treatment of DES, and (2) prevention of corneal trauma.

If it was not possible to prevent RCE, then it is necessary to use drugs that help rapidly normalizing the state of the corneal epithelium as well as relieving inflammation and pain.

Primarily, the use of lubricants is recommended to moisturize the eye and to prevent possible recurrence of corneal erosion. Regular instillations of "artificial tear" preparations without preservative should be used during the day, and gels and ointments should be used at night [2, 6, 10, 11, 15, 16]. If this therapy is ineffective in severe concomitant DES, punctal plugs are used [2]. In patients at risk of secondary bacterial infection, broad-spectrum antibacterial drugs are used as a short course (the use of ointments accelerates epithelialization, but in the case of using a bandage contact lens, low viscosity medications are chosen) or ophthalmic local antiseptics (e.g., picloxydine) are administered. To stop the inflammatory reaction and pain syndrome, the use of local non-steroidal anti-inflammatory drugs (NSAIDs) is permitted; however, similar to local anesthetics, they must be used with great caution and only in cases when they cannot be avoided, since both these groups slow down significantly the corneal epithelium regeneration [6, 11, 17]. Their use is absolutely contraindicated in patients with RCE that has developed against neurotrophic keratopathy background. With severe pain syndrome, a single oral dose of painkillers or NSAIDs or till the relief of pain can be considered in the absence of contraindications from the gastrointestinal tract.

Fujikawa and del Castillo concluded that another effective method of treatment for RCE could be the autologous serum use, as it can provide the eye surface with substances that contribute to the early recovery of the affected epithelium and saturation with vitamin A and epidermal growth factors due to the presence of fibronectin and other cytokines [18, 19].

A common method of treatment for RCE relapse, which accelerates visual rehabilitation and the healing process as well as reduces pain syndrome, is wearing of soft silicone hydrogel contact lenses (CL), selected in accordance with the rules of contact correction and allowed for long-term wearing (not removed at night). Kent et al. [20] and Poland and Kaufman [21] have suggested the therapeutic use of soft contact lenses with a significant disruption of the corneal epithelium structure, since they help protect the cornea from additional trauma during blinking movements of the upper eyelid, which accelerates the epithelialization process and prevents the recurrence of corneal erosion. Prolonged wear of a bandage contact lens after another episode of RCE is associated with fewer relapses. Moreover, Kent et al. [20] warn that long-term use of soft contact lenses can cause bacterial keratitis, corneal vascularization, and scarring; therefore, the initial assessment of risks of using contact lenses in treatment is recommended for each patient with RCE. In 2013, Ling et al. reported on the efficiency of treatment for RCE with the PROSE eco-prosthesis [22]. Various options for amniotic membrane transplantation are also widely used in the treatment of RCE. In the USA, the FDA model of the ProKera cryopreserved amniotic membrane is available and approved, which can be placed similarly to CL [42]. After achieving complete epithelialization of the cornea, to prevent relapses, in the global ophthalmic practice, hypertensive eye ointment (not available in the Russian Federation) is recommended at night to reduce the physiological edema of the corneal epithelium during sleep.

Dursun et al. propose to use additional drugs such as inhibitors of MMP-2 and MMP-9, acting on one of the links in the RCE pathogenesis [23]. The use of MMP-9 inhibitors is of especial significance in patients with

rosacea, since this group of patients demonstrated a significant increase in the level of this indicator, which determines (in conjunction with DMG and DES) a higher incidence of RCE in this patient population. For the same reason, systemic antibacterial tetracycline drugs (e.g., doxycycline) are usually included in the complex of conservative therapy for RCE in patients with rosacea, since they have a pronounced anti-inflammatory effect, as well as treatment for DMG, including instillation of glucocorticoids in low doses and of cyclosporin A [1]. The use of glucocorticoids in the treatment of patients with other RCE type is debated, since despite the good anti-inflammatory and anti-edema effect, they are able to slow down regeneration and cause the development of infectious complications and keratomalacia.

For case follow-up of the erosion area, description of its size in millimeters can be traditionally used, or the system of dividing the cornea into sectors similar to the 12-hour dial, which was proposed by Hykin et al. [6], can be applied, where 0–3 erosions are regarded as small, 4–6 as medium, 7–9 as large, and 10–12 as very large [6].

Surgical treatment of patients with RCE

The use of the above conservative methods of treating RCE enables in most cases resolution of all signs and ensures complete epithelialization of the cornea. Surgical methods of treatment should be used in absence of a positive effect from the therapy, frequent relapses that reduce the patient's quality of life, and significant decrease in visual acuity due to the development of irregular astigmatism and cicatricial haze of the cornea. The recurrence rate is also higher after conservative therapy than after surgical treatment [15].

In the development of ophthalmosurgical techniques in the case of RCE, a simple mechanical removal of the altered epithelium was initially used, under local anesthesia, with a scalpel or scarifier, often even behind a slit lamp. However, such a rough effect on the cornea slowed down epithelialization, and the frequency of relapses was quite high. Dua et al. [24] used successfully alcohol delamination for these purposes (removal of the corneal epithelium using a 20% alcohol solution) if other treatment methods were ineffective. However, this technique is associated with alcohol solution toxicity for the remaining corneal structures.

Among modern surgical techniques, abrasive resurfacing of Bowman's membrane with a diamond bur [1, 7, 25, 26] and excimer laser phototherapeutic keratectomy [1, 27, 28] are currently considered to be most effective in treating patients with RCE. Anterior stromal puncture, including the use of a neodymium YAG laser, although it was popular during its first emergence, has recently been used less and less because of obvious drawbacks, a number of limitations, and an unstable therapeutic effect.

In 1986, McLean published a study of the manifestations of RCE in patients with superficial non-penetrating corneal injuries. He was the first to suggest anterior stromal puncture to improve the adhesion of the anterior corneal epithelium due to the formation of additional scar tissue in loosely fixed places. During anterior stromal puncture, several small punctures are made through the epithelium and Bowman's membrane using a 25–27 G insulin needle under local anesthesia, sometimes just behind the slit lamp. These punctures stimulate the synthesis of type I collagen, which accelerates the restoration of the basement membrane and leads to local scarring of the cornea, providing better adhesion of the epithelium and basement membrane in these areas and forming certain anchors from cicatricial haze that should keep the epithelium in its place [29]. An increase in the accuracy of the procedure is possible with the use of fluorescein given its average effectiveness of 62%. Meanwhile, the use of this treatment method is possible only when the erosion is localized outside the optical zone of the cornea, since otherwise the induced cicatricial haze will affect the patient's visual functions. Recovery is faster when using a contact lens, but according to a number of researchers, the wearing period should not exceed 7 days [30].

A short-pulse Nd: YAG laser with an energy of 1.8–2.2 mJ could be used to perform anterior stromal puncture, which has been demonstrated by Geggel in the 1990s [31]. The efficiency of this technique is approximately 80%, and recurrences of erosions are more often registered when they are localized at a great distance from the puncture site, especially in case of epithelial dystrophies [29].

In 1987, Buxton and Constad [32] demonstrated high efficiency of superficial keratectomy with a diamond bur. Surgical removal of the epithelium activated the regeneration process, starting from a healthy peripheral edge, and dead altered cells are preliminarily removed over an area of 6–10 mm. Then, Bowman's membrane is uniformly ground with a diamond bur, and a bandage contact lens is applied. Various researchers reported that the effectiveness of this technique ranged from 85% to 97% [26, 33]. Abrasive resurfacing of Bowman's membrane with a diamond bur is more effective than conventional mechanical removal of the epithelium in reducing the number of relapses, but in the postoperative period, with excessive Bowman's membrane exposure, edema may occur, followed by cicatricial haze formation in the optical zone. In refractive surgery, this condition is referred to as "haze"; as a rule, the use of local glucocorticoids may minimize its manifestations [25]; nevertheless, the restoration of visual functions after this method of surgical treatment is usually slowed down.

In 1992, Gipson and Aitken proposed a method for treating patients with RCE, called phototherapeutic

keratectomy (PTK). The authors recommended using an excimer laser for this surgery, which allowed ablation of the altered corneal epithelium as accurately as possible and with minimal damage to the surrounding tissues. Scientists have concluded that partial removal of Bowman's membrane (5–10 μm) ensures the formation of a smooth bed, where epithelial cells gradually migrate [5, 10, 27, 34]. PTK is preferable for a large area of pathological changes in the epithelium, in the presence of subepithelial haze of the anterior stroma, which can also be removed during ablation. The method has proven itself as effective in the treatment of both traumatic and dystrophic RCE [27, 28, 34, 35]. In 2002, Maini and Loughnan [36] described a number of disadvantages of PTK, including pain syndrome in the postoperative period and the possibility of a hypermetropic shift. Nevertheless, with recent improvements in technique and emergence of topographic-oriented ablation methods, this type of surgical procedures has become one of the leading treatments after the failure of conservative therapy for RCE, and it is considered as safe and effective treatment method [7, 28]. The absence of the disease relapses after PTK varies from 69% to 100% [1, 27, 35, 36]. With residual astigmatism, it is subsequently possible to perform PTK with a refractive aim.

Most surgical methods for treatment of RCE are associated with the removal of altered corneal epithelium; therefore, in the postoperative period, a bandage contact lens is usually put on the cornea until the epithelialization process is completed, and instillations of broad-spectrum antibiotics and glucocorticosteroids are prescribed as postoperative therapy. Sridhar et al. [37] compared PTK and diamond bur resurfacing in patients with RCE of dystrophic origin and concluded that both methods are effective in treating this condition, although the formation of postoperative corneal haze in their work was quite more common with PTK.

The collagen crosslinking technique using ultraviolet irradiation and riboflavin as a photosensitizer, developed by Wollensak et al. in 2003 [38] for biomechanical stabilization of the cornea, was intended for the treatment of progressive keratectasias, but later, it was successfully applied in other pathological conditions such as infectious keratitis, corneal ulcers, and bullous keratopathy [39, 40]. The release of free oxygen radicals, which induce the formation of cross-bonds between collagen molecules, occurs as a result of interaction of ultraviolet radiation with riboflavin. The biological effects of corneal collagen crosslinking (CCC), such as an increase in the elastic modulus of the cornea, an increase in the force of its resistance to deformation, resistance to enzymatic action, and a pronounced antihydration effect, can be used in treatment of patients with RCE. In the literature, limited studies have focused on the CCC effect on the course of RCE [35, 41]; however, this method is of certain clinical interest. Since the standard protocols of the procedure for performing CCC include removal of the anterior corneal epithelium, this makes its use pathogenically justified in RCE, arising from pathological changes in the epithelial layer and its basement membrane. Salmon reported that crosslinking demonstrated 88.9% efficiency in the treatment of RCE associated with degenerative changes in the epithelium and corneal stroma [41].

This study aimed to examine retrospectively the results of the use of corneal collagen crosslinking in patients with RCE.

MATERIALS AND METHODS

The study was conducted in St. Petersburg City Diagnostic Center No. 7. It included 18 female patients (20 eyes) aged 30–66 years (mean age, 49.5 ± 10.69 years). All patients signed informed consent for participation in the study and personal data processing. The main criteria for inclusion were frequent relapses of the disease and absence of a persistent effect of conservative therapy (for at least 6 months). Patients with a corneal thickness less than 400 μm, subepithelial cicatricial haze of the anterior stroma in the optical zone, a history of herpetic keratitis, infectious or autoimmune diseases, moderate and severe DES, and history of surgical interventions on the cornea were not included.

CCC was performed from 2013 to 2019; the follow-up period differed for each patient, and ranged from 1 to 6 years (average, 2.6 ± 1.6 years). All patients underwent a comprehensive examination, which included biomicroscopy, ophthalmoscopy, ophthalmometry, refractometry, visual acuity testing, tonometry, perimetry, and ultrasound pachymetry. The CCC procedure was performed according to the Dresden protocol by the same surgeon using a UV X version 1000 device from IROC INNOCROSS (Switzerland) with a wavelength of 365 nm and a power flux density of 3 mW/cm^2. A 0.1% solution of riboflavin with 20% dextran (Dextralink, Ufa) was used as a photosensitizer.

After the surgery, all patients used silicone hydrogel contact lens until complete epithelialization and received instillations of levofloxacin q.i.d. for 7 days as well as an "artificial tear" preparation without preservative q.i.d. Data collected during the primary examination and case follow-up were analyzed. During the study, uncorrected visual acuity (UCVA) was assessed in all patients, as well as best corrected visual acuity (BCVA), pre- and postoperative astigmatism, and absence or presence of RCE (Table 1). Statistical data processing was performed in SPSS21 statistical package. The nonparametric Wilcoxon test was used for non-binary linked samples and McNemar's test for binary linked samples. The confidence interval was 0.05.

Table. Comparative data analysis

Таблица. Сравнительная оценка исследуемых показателей в динамике

Parameter	Before surgery	After surgery	*p*
Uncorrected visual acuity (UCVA)	0.45 ± 0.34	0.44 ± 0.30	0.746
Best corrected visual acuity (BCVA)	0.93 ± 0.09	0.97 ± 0.07	0.046
Sph (D)	2.05 ± 1.49	2.01 ± 1.47	0.502
Cyl (D)	0.63 ± 0.60	0.59 ± 0.52	0.587
Relapses in a year	3.65 ± 1.23	0	0.001

RESULTS AND DISCUSSION

Results obtained after analysis of CCC data revealed a significant increase in BCVA, absence of disease relapse (during the follow-up period), and of induced astigmatism. UCVA, the power of the spherical and cylindrical components did not change significantly. Corneal complications were not detected after the CCC procedure, although Elmoddather noticed a delayed recovery of corneal transparency (within 1 month) in 4 of 19 cases [36]. Compared with literature data, no relapse was recorded in our study group, although other authors reported relapse rate of 11%–27% [35, 41]; this is probably due to the selected group of patients and exclusion of pronounced cicatricial haze in the subepithelial anterior corneal stroma, which ensured the best effect of the technique chosen and the best result.

The literature describes one study with a small sample of patients (19 patients in each group) comparing the efficacy of CCC and PTK in the treatment of RCE [36], that is, RCE signs disappeared in 78% of the patients after PTK and in 73% after CCC surgery. The patients were satisfied with surgical treatment result, and no significant difference was found in the visual acuity of these two groups.

CONCLUSION

The analysis of the long-term results of CCC in the treatment of RCE helped establishing its positive therapeutic effect (cessation of relapses) and even revealed a minor increase in visual functions in a number of cases. The data obtained open additional prospects for studying the effect of CCC on the treatment of patients with RCE when other methods have not provided the desired result. Since in most RCE cases pathological changes in the cornea are concentrated at the level of its anterior epithelium and basement membrane, in the future, it is advisable to use modified crosslinking techniques that limit its effect in depth to avoid an adverse effect on stromal keratocytes.

The choice of a surgical method for treating RCE is always individualized and depends not only on the cause of the disease, area, depth, and localization of the corneal pathological changes, as well as concomitant ophthalmic conditions, but also on the technical equipment of a particular ophthalmological clinic and its accessibility for the patient. Thus, grinding with a diamond bur and anterior stromal puncture are considered relatively affordable methods of treatment, while PTK and CCC, especially femtosecond laser-assisted, require expensive equipment.

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