

Secondary dry eye syndrome after keratorefractive surgery and approaches to its treatment and prevention

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The article reviews the particularities of development and pathogenesis of secondary dry eye syndrome (DES) after refractive surgeries including a complex of problems related to changes in tear film content, damage of eye surface and neurotrophic epitheliopathy. Additionally, modern algorithms of treatment and prevention of secondary DES in patients after refractive surgeries are described. Despite the transient nature of the changes, excimer-laser surgery can lead to lasting deficiencies of eye surface in some patients. Therefore, intensive and early treatment of secondary DES during the early follow-up period after refractive surgery may significantly reduce risks of tear dysfunction and neurotrophic epitheliopathy development in the long term.

Keywords: secondary dry eye syndrome, refractive surgery, artificial tears, cationorm.

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At the present time, a great number of refractive surgery operations is performed all over the world, thus every year more than 1 million LASIK (Laser-assisted *in situ* keratomileusis) surgeries are done in the USA alone [1]. In this context, about 98.5% of patients are satisfied with the operative outcome after 7 and more months, while the number of complications is very low [2].

The most common complaints are eye dryness and irritation which present themselves in both the early and late postoperative period. As a rule, dry eye symptoms appear on day one after the operation and disappear by month 6 to 9 after the intervention. According to I. Toda, neurotrophic epitheliopathy symptoms are observed in 50% of patients at week one after LASIK, in 40% — during the first month, and only in 20% — throughout six months after the operation [3].

However, in some cases, when dry eye syndrome (DES) signs are present, not all of patients make relevant complaints. This is evidence of a qualitatively different nature of DES after keratorefractory surgeries.

Traditionally, DES is associated with a reduction in tear quantity, but presently it is accepted that this term includes a reduction in capacity to maintain the balance of tear components [4, 5].

In 2017, the latest version of the DES definition was formulated at the Dry Eye WorkShop (DEWS II) as follows: “Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.” [6].

This definition enables to explain not only the primary nature but also secondary nature of DES development, for example, after keratorefractive interventions,

operations on the cornea or after corneal collagen cross-linking [7].

Pathogenesis and secondary DES manifestations after keratorefractive interventions. In 2001, S. Wilson and R. Ambrosio noted that transient dry eye symptoms, sometimes accompanied by blurred vision, epithelial erosions on the corneal flap with relatively normal tear production developed in many patients after LASIK surgery [8]. In this context, these problems disappeared almost in all cases within 6 months. In this connection, the term “neurotrophic epitheliopathy” was proposed in order to describe this phenomenon; it implies that these transient alterations of the ocular surface are secondary to loss of trophic influence on the corneal epithelium caused by cutting its nerve endings.

At the present time, neurotrophic epitheliopathy is a well known condition which is associated with complaints about typical dry eye symptoms and vision fluctuations [9]. Most patients seem to suffer from neurotrophic epitheliopathy after LASIK surgery, even without previous lacrimal dysfunction, in the early postoperative period.

Secondary DES manifestations after keratorefractive surgeries don't include only neurotrophic epitheliopathy. They appear over the entire ocular surface, including the conjunctiva, as during surgery the blepharostat and the vacuum ring of a microkeratome or femtosecond laser exert a damaging effect on these structures, thus affecting the normal physiological processes in them [10].

When performing excimer laser interventions, there is loss of conjunctival goblet cells [10–12], and their den-

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sity decreases immediately after surgery. As a result, mucin production decreases, which in its turn results in reduced tear film stability. These alterations are most marked in patients with chronic DES symptoms [11]. In this context, in order to return the density of goblet cells to preoperative values, it may take about 6 months.

Cutting corneal nerves by using a microkeratome or femtosecond laser [13] with subsequent ablation of sensitive corneal nerves usually results in corneal hypoesthesia immediately after surgery, causing direct and indirect effects on the ocular surface [14, 15]. This damaging effect produced on fibres seems to play a key role in the early development of

LASIK-induced epitheliopathy and lacrimal dysfunction [16].

According to the results of various studies, corneal sensitivity recovers progressively, reaching its preoperative or “normal” values in 6–12 months, if it is measured with a Cochet-Bonnet esthesiometer [17, 18], and in 2 years, if it is measured with an air esthesiometer [19]. Other authors think that corneal sensitivity does not return to preoperative or “normal” values not only 6 months [20], but also 16 months after surgery [21].

Confocal microscopy after LASIK surgery confirms that the density of corneal nerve endings decreases in the early postoperative period and increases in the course of time, although at a slower rate compared to that of corneal sensitivity recovery [22]. S. Lee et al. found out that the density of subbasal nerve fibres was close to zero during six months after LASIK surgery [23]. B. Lee et al. discovered that one year after surgery the number of subbasal and stromal nerves in the corneal flap was reduced by half compared to that before surgery [24]. Besides, corneal sensitivity after excimer laser surgery returns to its “normal” values in the period from 6 months to 2 years [25] (depending on the method of measurement used), the density of subbasal nerves does not return to its preoperative values in 2 years [26], 3 years [27] and even in 5 years [22], according to the confocal microscopy results.

There is no doubt that the injuries of the ocular surface described above and the denervation of subbasal and stromal corneal layers certainly result in changes in the composition and stability of the tear film [28].

The time of tear fluorescein clearance after excimer laser vision correction increases, which may be determined by a lesser blinking rate [29]. I. Toda et al. found out that the blinking rate in patients after LASIK surgery was reduced by more than 40%, and a statistically significant difference between average values before and after surgery remained constant during one year [30].

After LASIK surgery, the tear break-up time decreases [31], while the results of the Schirmer’s test vary from no changes to marked changes [32]. In this context, reduced basal secretion, tear production and tear break-up time may last for months, and sometimes for a longer time [33]. In addition, tear hyperosmolarity is observed in patients after LASIK surgery and photorefractive kera-

tomy (PRK) during more than 6 months [34], but there are very few studies.

Dry eye syndrome treatment after keratorefractive surgeries. The purpose of secondary DES treatment is to recover ocular surface homeostasis, remove DES symptoms and, finally, improve patients’ quality of life [35, 36].

The approach to secondary DES treatment should be individual and based on three primary points [37]. First of all, this is risk factors for DES development after keratorefractive surgery, which are: existence of DES before surgery; wearing contact lenses for a long time prior to surgery; a high degree of ametropia; administration of medicinal products causing DES development; initial disease including DES [31]. In the second place, it is necessary to take into account such relevant complaints as sharp pain and dryness, discomfort, fatigue and redness of the eye, occasionally lacrimation [38, 39]. And the third point is signs of epitheliopathy which may be viewed biomicroscopically [40].

In addition, in selecting the optimal treatment of secondary DES, it is necessary to give preference to preservative-free medicinal products, especially if benzalkonium chloride is used, since many studies have proved an irritating effect of this substance on the cornea [41], while a surgical injury itself does not result in ocular surface damages. As a consequence, the response to tear substitute therapy may be reverse, and instead of relieving DES symptoms, patients may feel a greater degree of discomfort immediately after administering eye drops.

The not less important point in secondary DES treatment is the time factor, as the primary processes of recovery of the tear film composition, ocular surface condition and corneal reinnervation are completed in the period from 6 to 12 months after keratorefractive surgery [42].

In the early postoperative period, frequently enough patients make complaints about permanent eye dryness, especially in the morning, epitheliopathy and “floating vision” signs are observed, and, as a rule, in such cases there are risk factors for DES development reported in the anamnesis. With such a clinical pattern, treatment should be intensive and complex.

Normally, artificial tear products — called tear substitutes — are used as first choice medications for treatment of DES manifestations [43], and, if it is necessary, medicinal products from other groups are added to them, most often these are keratoprotectors [44] or gel-based products for ensuring prolonged moisturising, including during the night time [45]. As eye gels, products containing several moisturizing components at high concentrations could be marked out. For example, Oftage1® contains carbomer at the maximum concentration — that is 0.25%, as well as polyvinyl alcohol, this composition enables the product to show moisturizing effect, including in case of relatively infrequent instillation (beginning from once daily).

Artificial tear products may contain both various isolated polymers (polyvinyl alcohol [46], povidone [47], cellulose derivatives [48], hyaluronic acid [49, 50]) and combinations with other components — electrolytes, vitamins, osmoprotectors and lipids [51, 52].

In this context, although artificial tear products are considered as a reference medication in treatment of DES, there is no data on large randomized controlled studies to assess the effectiveness of the whole variety of tear substitutes available in the market. Small (local) randomized studies showed that this group of products increases tear film stability, restores the ocular surface, enhances contrast sensitivity and quality of vision and thus improves patients' quality of life [53–5].

Absolutely new eye drops launched in the market relatively not long ago — such as Cationorm — may serve as an alternative option. As a matter of fact, this is a cationic emulsion created according to the Novasorb® technology. This product contains positively charged nanoparticles with an oil core, which electrostatically bind to the negatively charged ocular surface [56].

Cationorm is rapidly distributed over the ocular surface immediately after instillation and produces a curing effect on all three layers of the tear film. It recovers the lipid layer, stabilizes the tear film, increasing its break-up time, and reduces tear evaporation. In addition, it restores the aqueous layer, ensuring sufficient moisturizing for the underlying structures, as well as producing an osmocorrective and osmoprotective effect, thus protecting ocular surface cells. Due to bioadhesion to the ocular surface, the product contributes to mucin layer recovery and reduces friction of eyelids against the ocular surface when blinking [57, 58].

In addition, a study conducted to assess the influence of cationic emulsion on cornea healing in patients who

underwent photorefractive keratectomy showed that significantly better re-epithelization results were achieved one week after initiating therapy with Cationorm in comparison with hyaluronic acid [59]. Furthermore, Cationorm does not contain preservatives, which reduces to a minimum the risk of toxic effects on the ocular surface.

However, in the late postoperative period, when a secondary DES clinical pattern is not well expressed or practically is not apparent, tear substitutes based on hyaluronic acid may be more effective for prevention purposes. In this context, products with the greatest molecular mass will offer an advantage, which enables them to remain for more time over the ocular surface. In addition, a high molecular mass ensures marked thixotropic properties, owing to which such medicinal products are well tolerated by patients [5, 60]. Ocutears®, preservative-free ophthalmic solution containing 0.15% hyaluronic acid with superhigh molecular mass, which enables the product to produce a more prolonged moisturizing effect, may serve as an example.

Accordingly, secondary DES after keratorefractive interventions includes a set of problems associated with changes in the tear film composition, ocular surface injury and neurotrophic epitheliopathy development. Notwithstanding the fact that these changes have a transient nature, excimer laser surgery may result in persistent functional impairments of the ocular surface in some patients. Therefore, intensive and timely treatment of DES in the early period after surgery may considerably reduce the risk of developing lacrimal dysfunction and neurotrophic epitheliopathy in the long term.

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