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Research Article

Possibilities of reparative therapy in the treatment of patients with xerotic changes in the cornea

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ABSTRACT

In recent years, in the treatment of patients with dry eye syndrome, drugs that, along with moisturizing, also have specific metabolic properties, due to the additional medicinal ingredients contained in them, deserve more and more attention. The article presents comparative data on the preparations of "artificial tears" and so-called keratoprotectors registered in Russia. In addition, a number of experimental and clinical studies by domestic authors evaluating the pharmacological and clinical effect of the new keratoprotector *SPHERO*®oko were reviewed. Much attention is also paid to the consideration of the original direction of *SPHERO*®oko application — its introduction into the corneal stroma (together with a dye) for cosmetic and functional keratopigmentation in the presence of extensive iris defects. The authors of the literature review, taking into account the results of numerous experimental studies and some clinical observations, believe that the use of *SPHERO*®oko has quite great opportunities in the complex treatment of xerotic changes of the cornea and conjunctiva. At the same time, it is of interest to continue the research on the possibilities of intrastromal administration of colored *SPHERO*®oko for keratopigmentation in the presence of extensive iris defects.

Keywords: dry eye syndrome; keratoprotectors; artificial tear preparations; *SPHERO*®oko.

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Научная статья

Возможности репаративной терапии в лечении пациентов с ксеротическими изменениями роговицы

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АННОТАЦИЯ

В последние годы в лечении пациентов с синдромом сухого глаза всё большего внимания заслуживают препараты, обладающие, наряду с увлажняющими, и специфическими метаболическими свойствами, благодаря содержащимся в них дополнительным лекарственным ингредиентам. В статье приведены сравнительные данные зарегистрированных в России препаратов «искусственной слезы» и так называемых кератопротекторов. Кроме того, рассмотрен ряд экспериментальных и клинических исследований отечественных авторов, оценивающих фармакологический и клинический эффекты нового кератопротектора *СФЕРО*®око. Большое внимание уделено рассмотрению оригинального направления его применения — введение в строму роговицы (совместно с красителем) в целях косметической и функциональной кератопигментации при обширных дефектах радужки. Авторы обзора литературы, учитывая результаты выполненных многочисленных экспериментальных исследований и отдельные клинические наблюдения считают, что применение *СФЕРО*®око имеет достаточно большие перспективы в комплексном лечении ксеротических изменений роговицы и конъюнктивы. При этом представляет интерес продолжение исследований возможностей интрастромального введения окрашенного препарата *СФЕРО*®око в целях кератопигментации при обширных дефектах радужки.

Ключевые слова: синдром сухого глаза; кератопротекторы; препараты «искусственной слезы»; *СФЕРО*®око.

Как цитировать

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ЭКО•ВЕКТОР

In recent years, the treatment of dry eye syndrome has moved beyond the use of artificial tears for hydrating the ocular surface to include reparative therapy for xerophthalmic changes [1].

However, the boundary between tear replacement and reparative therapy is blurred. Ocular surface hydration alone helps to improve metabolic processes in xerophthalmic cornea and conjunctiva [2]. This potentially promotes conjunctival gland secretion of mucins and the aqueous component of the tear film and glycocalyx formation of corneal and conjunctival epithelial cells [1, 2]. In addition, artificial tear therapy helps to reduce the osmolarity of the tear film, thus preventing and alleviating hyperosmolar stress and reducing the severity of inflammation in the ocular surface tissues. This, in turn, promotes reparative processes [1, 2].

Moreover, many polymeric bases of artificial tears also have reparative properties (natural mucopolysaccharides such as high molecular weight hyaluronic acid, hydroxypropyl guar, chondroitin sulfate, some synthetic polymers such as polyvinyl alcohol, etc.) [1, 3–8].

Meanwhile, there is also a growing interest in pharmaceutical products (ophthalmic solutions, gels, and ointments) that, in addition to their moisturizing properties, have specific metabolic properties due to additional active ingredients [1–4]. According to the Anatomical Therapeutic Chemical Classification (ATC), most of them are classified as corneal moisturizers and corneal protectors. However, with regard to the above-mentioned conditions, the boundaries between them and "classic" artificial tears are vague (see figure)*.

It seems more logical to evaluate all these compounds based on their pharmacological properties rather than the said conventional ATC classification. The situation is further complicated by the categorization of products as either drugs or medical products. Most of such formulations fall into the latter category. With these caveats in mind, we consider the potential of reparative therapies for the xerophthalmic changes that have emerged in recent years.

The table lists artificial tears and corneal protectors that have proven metabolic properties in addition to moisturizing properties.

In 2015, the range of such agents was expanded with the Russian approval of *SPHERO*®oko (BIOMIR Servis JSC, Russia), a multicomponent hydrogel biomimetic of the extracellular matrix [9].

SPHERO®oko is a biopolymer gel derived from the hydrolysate of embryonic or postnatal animal collagen tissues with minimal immunogenicity. The product contains both major components of the extracellular matrix (collagen, proteoglycans, and glycoproteins) and other

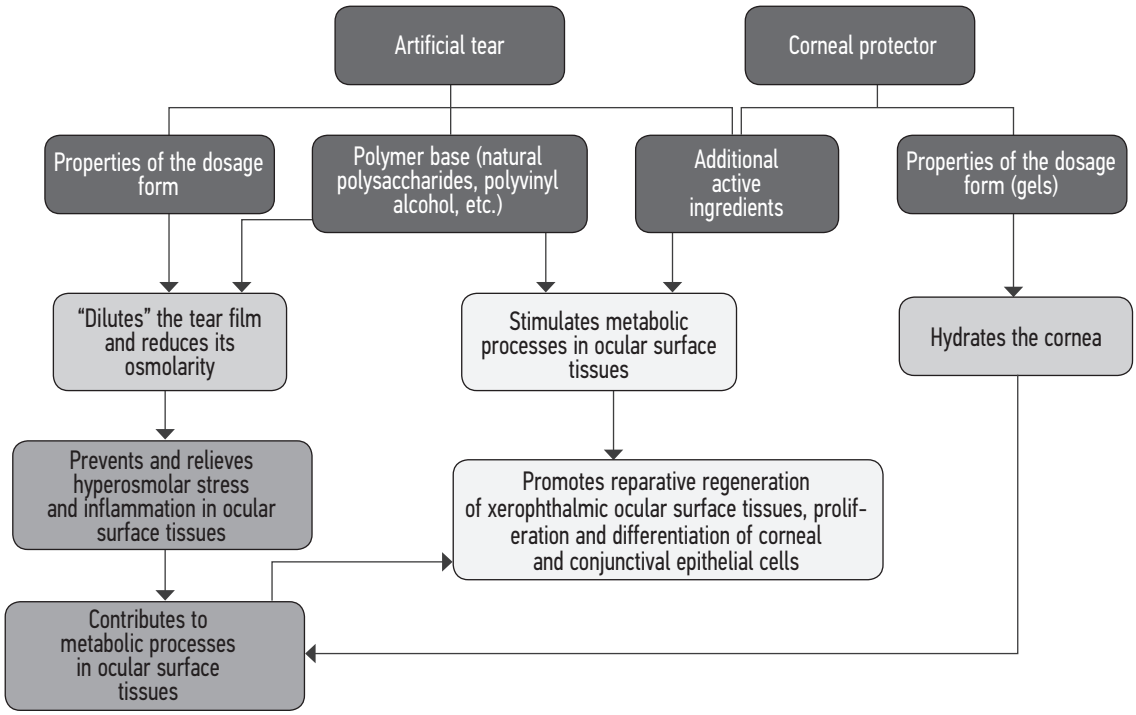

Figure. The mechanism of achieving a metabolic effect of some artificial tears and keratoprotectors
Рисунок. Механизм достижения метаболического эффекта некоторых препаратов «искусственной слезы» и кератопротекторов

*rlsnet.ru/atc [online]. Russia State Registry of Medicines® [Accessed on January 14, 2024]. Available at: https://www.rlsnet.ru/atc; rlsnet.ru/ [online]. Russia State Registry of Medicines® [Accessed on January 14, 2024]. Available at: https://www.rlsnet.ru/taa/groups/medicinskie-izdeliya-sredstva-uxoda-i-gigieny-10

Table. "Artificial tears" and so-called keratoprotectors with reparative properties, registered in Russia

Таблица. Зарегистрированные в России препараты «искусственной слезы» и кератопротекторы, обладающие репаративными свойствами

Active substance	Trade name	Manufacturer
Dexpanthenol 5%	Corneregel*	Bausch+Lomb
	Dexpantel*	Tatchempharmpreparaty JSC
Dexpanthenol 2%	Systane® Ultra Plus	Alcon
	Hylozar-Comod®*	Ursapharm
	Hypromeloza-P*	Unimedpharma
	Optinol® Soft recovery	Jadran
Dexpanthenol 1%	Stillavit®	Stada
Sodium hyaluronate (0.1%–0.4%)	Artelac® Splash, Artelac® Splash Uno, Artelac® Balance, Artelac® Balance Uno, Artelak® Night, Oxyal	Bausch+Lomb
	Hylo-Comod®, Hylozar-Comod®, Hyloparin-Comod®	Ursapharm
	Hylabak	Thea
	Vismed, Vismed light, Vismed multi, Vismed gel	TRB Chemedica
	Ocutears® Hydro+	Santen
	Gylan Comfort, Gylan Ultra Comfort	Solopharm
	Systane® Ultra Plus	Alcon
	Eyestill	Sifi, NovaMedica
	Optinol®: Express Moisture (0.21%) and Deep Moisture (0.4%)	Jadran
Chondroitin sulfate	Stillavit®	Stada, Oftalm-Renessans
	Ocvis	Dubna-Biofarm LLC
Hydroxypropyl guar	Systane® Ultra, Systane® Ultra (monodoses), Systane® Ultra Plus, Systane® Balance, Systane® Gel	Alcon
TS-polysaccharide	Visine® True Tears, Visine® True Tears (1 day)	Johnson & Johnson
Vitamin A palmitate	VitA-POS®	Ursapharm
Heparin	Parin-Pos®, Hyloparin-Comod	Ursapharm
Deproteinized hemodialysate	Solcoseryl®* (state marketing authorization expired in 2022)	Legacy Pharmaceuticals Switzerland
Glycoprotein 0.01%	Adgelon®*	Endo-Pharm-A CJSC
Glycosaminoglycans, sulfated 0.01%	Balarpan®*	Scientific Experimental and Production Base "MNTK "Eye Microsurgery"
Collagen-containing extract (of animal origin)	*SPHERO*®oko	BIOMIR Servis JSC

*Regenerants and reparants and/or corneal protectors.

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biologically active substances, including peptides, amino acids, uronic acids, monosaccharides, growth factors, etc.

The multi-component nature of *SPHERO*®oko increases the metabolic activity of the epithelial cells of the ocular surface, promotes their proliferation and differentiation, and ultimately accelerates the reparative regeneration of the xerotic tissues of the cornea and conjunctiva. In addition, *SPHERO*®oko has anti-inflammatory, anti-congestant, and tear-substitution activities, and prevents corneal neovascularization, etc. [10].

SPHERO®oko is indicated for use in recurrent corneal erosion, filamentary keratitis, toxic corneal erosion, keratoconjunctivitis sicca, as well as for wearing orthokeratological contact lenses (the gel is administered under the orthokeratological contact lenses).

Numerous Russian experimental and clinical studies have demonstrated the pharmacological and clinical effects of *SPHERO*®oko and evaluated its tolerability in patients.

In 2017, I.A. Pronkin demonstrated the pharmacological effect of the study corneal protector in a rabbit model of grade III alkali corneal burn [11]. The combined use of the corneal epithelial protector *SPHERO*®oko resulted in a more structured and anatomically correct healing of the cornea compared to other metabolic products.

In addition, further clinical observations demonstrated the efficacy of the study formulation (in combination with 5% dexpanthenol) in patients with recurrent corneal erosion and filamentary keratitis. Addition of *SPHERO*®oko to the treatment regimen accelerated corneal epithelialization by an average of 41.5% in patients with recurrent corneal erosion and provided epithelial filament resorption in patients with filamentary keratitis. In addition, the potential of using the study corneal protector with a bandage soft contact lens was investigated [11].

Besides, initial positive results with *SPHERO*®oko were obtained in corneal erosions of various origins, when used as a component of local metabolic combination therapy after keratorefractive surgery (radial keratotomy) [12] and as reparative monotherapy after metaherpetic keratitis [10]. During 2 weeks of treatment in the first case and 1 month of treatment in the second case, complete corneal epithelialization and resolution of clinical symptoms of corneal erosion were achieved [10, 12].

We also introduced *SPHERO*®oko into our clinical practice in 2021. Our studies evaluated the potential of its use in the combination therapy in children and adults with stage 2 neurotrophic keratopathy (Mackie classification [13]) associated with extensive persistent corneal erosion (4 patients, 6 eyes) [14].

To summarize, after four applications in the conjunctival sac over 3 weeks, *SPHERO*®oko showed a tendency towards corneal epithelialization in all cases, and the originally planned corneal amnioplasty was cancelled. Moreover, all patients tolerated the conservative therapy well.

One of the original issues of *SPHERO*®oko is injection into the corneal stroma (using inorganic toner as dye) for cosmetic purposes and functional corneal pigmentation of extensive iris defects [15]. Using human corneal cultures, S.B. Izmailova et al. [15] demonstrated that an intracorneal colored gel implant based on *SPHERO*®oko was best suited for these purposes. Its structure was more compact and more dense compared to similar experimental products (based on sodium hyaluronate and hydroxypropyl methylcellulose) and met the requirements. The authors plan to continue these *in vivo* animal studies [15].

Based on extensive experimental data and clinical observations, *SPHERO*®oko has great potential for use in the combination treatment of corneal and conjunctival xerophthalmic changes. It is expedient to further explore the potential of intrastromal injection of colored *SPHERO*®oko for cosmetic and functional purposes.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published, and agree to be accountable for all aspects of the study. Personal contribution of each author: V.V. Brzeskii — concept and design of the study, editing; V.V. Brzeskii, V.A. Bobryshev — collection and processing of material, writing the text.

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