ABSTRACT

Dry eye syndrome is one of the main problems of modern ophthalmological pathology. Although the treatment of dry eye syndrome has made great strides, the development of new treatments continues to be a major challenge for scientists and ophthalmologists around the world. The development of highly effective and safe eye drops is especially important. The aim of the article is to conduct research on new eyedrops called Regenopia – the unique combination of three active substances: sodium hyaluronate, trehalose, and D-panthenol in the treatment of DED. Clinical observation of 128 patients (256 eyes) (85 women and 43 men 18-60 years age group with DED (patients with any chronic or autoimmune diseases were excluded from the research) treated with Regenopia was conducted from February 1-st to May 30-th, 2023. DED was diagnosed by anamnesis and instrumental clinical investigations (Visometry, Biomicroscopy, Schirmer’s test, Tear Break up time (TBUT)). Moderate dry eye - 75% (192 eyes), severe dry eye - 25% (64 eyes). In 24 eyes Superficial Punctate Keratitis (SPK) was determined after examination of the epithelial layer of the cornea and conjunctiva. One drop of Regenopia was instilled 3 times a day in both eyes by patients (in cases of SPK complex method of treatment was prescribed) and patients were called for a repeat visit in 3 weeks and 6 weeks after the start of treatment. The condition was assessed using the same methods as at the time of diagnosis. The bioprotective, osmoprotective, regenerative properties of trehalose significantly enhance hyaluronic acid’s ability to provide effective hydration and long-term symptom relief along with the regenerative action of dexpanthenol. Using Regenopia significantly reduced the intensity of symptoms, increased the patient’s ability to work, and improved the quality of life, which allows us to recommend Regenopia as an effective, safe and reliable treatment for moderate to severe dry eye disease.

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KEYWORDS: dry eye disease, dry eye syndrome, dry eye disease, treatment, Regenopia, sodium hyaluronate, trehalose, and D-panthenol

One of the most common ophthalmic syndromes, accompanied by pathological changes in the ocular surface and a violation of the homeostasis of the tear film, is dry eye disease (DED). The concept of ocular dryness has changed over the course of history. In Hippocratic times the term xerophthalmia (in Greek, dry eye) was applied only to absolute ocular surface dryness with corneal blindness. Historically the term “Dry Eyes” was first introduced in 1950 by Andrew De Roetth for any type of quantitative lacrimal deficiency, which little by little was completed with the concepts of aqualoiness, mucodeliness, and lipodeliness [1]. The first definition of dry eye was published in the report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye in 1995 [2]. It was the first formal attempt to define and classify DED, in addition to reviewing its treatment, management, and design of clinical trials [3]. At this stage dry eye was termed a “disorder” of the tear film with signs and symptoms attributed to tear deficiency or excessive evaporation. The NEI/Industry definition stated: Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpapillary ocular surface and is associated with symptoms of discomfort [2]. This definition lacked a description of any specific pathophysiologic basis. Nevertheless, the report provided a blueprint for clinical and basic research that would stimulate the field to the next level. Discussion regarding the appropriate definition for dry eye followed in 2007 with the Tear Film and Ocular Surface Society (TFOS) publication of the Report of the TFOS International Dry Eye Workshop that has become widely known as TFOS DEWS [4]. The workshop consisted of 58 members from 11 countries, had seven subcommittees, and its report was 140 pages in length [3]. The first TFOS DEWS updated definition of dry eye was published in 2007 [5]. This was the first time that dry eye had been identified as a disease, with many underlying causes, that was deemed to result in symptoms and signs, in association with tear film hyperosmolarity and ocular surface inflammation. Ten years later in 2017 owing to the growing body of literature, increased clinical data, and clinical, pharmaceutical industry interest in DED, TFOS DEWS II published the third and the latest extensive multipart report on DED – a gold standard DED definition and diagnostic criteria for ophthalmologists to differentiate DED from other ocular surface disorders [3, 6-15]. A two-year effort for 12 Subcommittees made up of 150 clinical and basic research experts from 23 countries, who used an evidence-based approach and open communication, dialogue, and transparency to achieve a global consensus concerning multiple aspects of dry eye disease has led to the creation and publication of substantial report [3]. One of the most important updates from TFOS DEWS I to TFOS DEWS II was the definition of dry eye disease. The newly developed TFOS DEWS II definition is centered on the clinical effects and associated signs. It states: 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]. Christopher E.
Starr (2017), in the article “TFOS DEWS II: What’s New?” highlights some of the key tenets of the TFOS DEWS II report: the inclusion of the phrase “loss of homeostasis”; the tear film consists of only two layers: a thin lipid layer on top and a mixed mucoaqueous layer underneath; the lipid layer, may be important in preventing tear evaporation; the mucoaqueous layer plays a role in reducing evaporative forces as well. Traditionally DED was thought of as comprising two distinct primary subtypes: aqueous-deficient dry eye and evaporative dry eye. Interestingly, with the TFOS DEWS II report, all dry eye becomes evaporative at some point and the two subtypes are thought to exist on a continuum. Goblet cell loss is a feature of all forms of dry eye. Both aqueous-deficient and evaporate are still used to identify the primary initiating cause of DED for treatment purposes, but all DED will ultimately show characteristics of evaporative DED. The new definition for the first time clarifies, based on recent peer-reviewed evidence, that tear film hyperosmolarity, instability, and ocular surface inflammation play etiologic roles, along with the addition of neurosensory abnormalities [16]. Advances in understanding of the risk factors, etiology and pathophysiology of DED have contributed to an evolution in treatment strategies over time. Female sex is a demonstrative risk factor for DED across virtually every study worldwide. It was postulated from studies that DED occurs more frequently in women than men. This is attributed in large part to the effects of sex steroids (e.g. androgens, estrogens), hypothalamic-pituitary hormones, glucocorticoids, insulin, insulin-like growth factor 1, and thyroid hormones, as well as to the sex chromosome complement, sex-specific autosomal factors and epigenetics (e.g. microRNAs), but anatomic differences matter as well. In addition to sex, gender also appears to be a risk factor for DED. Sex and gender are distinct entities in the medical literature. Sex is based on biological characteristics, and gender is based on socially accepted characteristics. Words “gender” and “sex” are often used interchangeably, but they have distinct meanings. “Gender” refers to a person’s self-representation as a man or woman, whereas “sex” distinguishes males and females based on their biological characteristics [12]. The female gender is stereotypically associated with a greater willingness to report pain, whereas the masculine stereotype is traditionally more stoic [16]. Both gender and sex affect DED risk. Overall, sex, gender and hormones play a major role in the regulation of ocular surface and adnexal tissues, and in the difference in DED prevalence between women and men. Future research is needed to advance our understanding of the interrelationships between sex, gender, hormones and DED [12]. The TFOS DEWS II recommendation for eye care providers is to take both sex and gender into consideration when managing DED [16]. The epidemiology of DED continues to be a challenge due to the lack of a standardized worldwide definition and study criteria. TFOS conducted a meta-analysis of the world literature and found that the prevalence of DED ranged from 5% to 50%. The prevalence of meibomian gland dysfunction was between 30% and 68% [7,16]. The knowledge of the risk factors for DED was assessed and summarized by Fiona Stapleton et al., (2017) (see Table 1) [7].
Table 1. Risk factors for dry eye disease [7]

<table>
<thead>
<tr>
<th>Consistenta</th>
<th>Probableb</th>
<th>Inconclusivec</th>
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<tbody>
<tr>
<td><strong>Non-modifiable</strong></td>
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</tr>
<tr>
<td>Aging</td>
<td>Diabetes</td>
<td>Hispanic ethnicity</td>
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<td>Female sex</td>
<td>Rosacea</td>
<td>Menopause</td>
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<tr>
<td>Asian race</td>
<td>Viral infection</td>
<td>Acne</td>
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<td>Meibomian gland dysfunction</td>
<td>Thyroid disease</td>
<td>Sarcoïdosis</td>
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<td>Connective tissue diseases</td>
<td>Psychiatric conditions</td>
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<td>Sjogren Syndrome</td>
<td>Pterygium</td>
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<tr>
<td><strong>Modifiable</strong>:</td>
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<tr>
<td>Androgen deficiency</td>
<td>Low fatty acids intake</td>
<td>Smoking</td>
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<td>Computer use Contact lens wear</td>
<td>Refractive surgery</td>
<td>Alcohol</td>
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<td>Hormone replacement therapy</td>
<td>Allergic conjunctivitis</td>
<td>Pregnancy</td>
</tr>
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<td>Hematopoietic stem cell transplantation</td>
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<td>Demodex infestation</td>
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<tr>
<td><strong>Environment</strong>:</td>
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</tr>
<tr>
<td>pollution, low humidity, sick building syndrome</td>
<td></td>
<td>Botulinum toxin</td>
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<td><strong>Medications</strong>:</td>
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<tr>
<td>antihistamines, antidepressants, anxiolytics, isotretinoin</td>
<td>anticholinergic, diuretics, betablockers</td>
<td>multivitamins, oral contraceptives</td>
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a - Consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

b - Suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

c - Inconclusive evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale.

The change in understanding of dry eye syndrome led to the development of new and more effective medications [17]. The members of the Management and Therapy Subcommittee undertook an evidence-based review of current dry eye therapies and management options and summarized them in TFOS DEWS II Management and Therapy Report [13]. The goals of this committee were to review appropriate methods for the management of DED and recommend a strategy for their clinical application, based on an evidence-based review of the literature. The level of evidence for supporting data from the literature was evaluated according to the modified American Academy of Ophthalmology Preferred Practices guidelines (Table 2).

Wherever possible, peer-reviewed publications, rather than abstracts, have been used by Lyndon Jones, et al. (2017) to guide management recommendations [13]. The report was reviewed by all subcommittee members and made available for constructive critique by the entire Tear Film and Ocular Surface Society’s Dry Eye Workshop II (TFOS DEWS II) membership. Comments and suggested revisions were discussed by the subcommittee members...
and incorporated into the report, where deemed appropriate by consensus. Following this extensive review, it became clear that many of the treatments available for the management of dry eye disease lack the necessary evidence to support their recommendation, often due to a lack of appropriate randomization or controls and in some cases due to issues with selection bias or inadequate sample size [13]. While this exercise indicated that differentiating between aqueous-deficient and evaporative dry eye disease was critical in selecting the most appropriate management strategy, it also highlighted challenges, based on the limited evidence currently available, in predicting relative benefits of specific management options, in managing the two dry eye disease subtypes. Further evidence is required to support the introduction, and continued use, of many of the treatment options currently available to manage dry eye disease, as well as to inform appropriate treatment starting points and understand treatment specificity in relation to dry eye disease subtype [13].

Historically, DED was considered to be largely due to tear insufficiency and was treated by prescribing tear replacement products or by conserving the tears via punctal plugs. More recent treatments have included the use of methods to stimulate tears. There are several approaches in DED treatment: tear replacement, conservation, stimulation approaches etc. Tear replacement with ocular lubricants is a mainstay of DED therapy. Over-the-counter (OTC) products are often termed “artificial tears” which attempt to replace and/or supplement the natural tear film. However, these products do not target the basic pathophysiology of DED. Tear substitutes aim to target layers of the tear film. There are relatively few randomized controlled trials (RCTs) that have

Table 2. Research evidence grading scheme.

<table>
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<th>CLINICAL STUDIES</th>
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<tr>
<td><strong>Level 1</strong></td>
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<tr>
<td>Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
</tr>
<tr>
<td>Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more center, or a well-designed study accessible to more rigorous statistical analysis</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
</tr>
<tr>
<td>Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion</td>
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<th>BASIC SCIENCE STUDIES</th>
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<tr>
<td><strong>Level 1</strong></td>
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<tr>
<td>Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
</tr>
<tr>
<td>Preliminary or limited published study</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
</tr>
<tr>
<td>Meeting abstracts or unpublished presentations</td>
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compared the relative superiority of a particular OTC product to others for DED therapy [18]. While artificial tears may be effective for treating DED, there was still a need for future research about the effectiveness of individual OTC artificial tear formulations. While ocular lubricant formulations may vary, most share similarities in their major components. The most abundant component in lubricant eye drops is the aqueous base. To enhance lubrication and prolong the retention time on the ocular surface, a variety of viscosity-enhancing agents are frequently incorporated. Viscosity enhancers are considered beneficial to the ocular surface in DED through a range of reported mechanisms. These include increasing tear film thickness, protecting against desiccation, promoting tear retention at the ocular surface, maintaining physiological corneal thickness, improving goblet cell density and relieving dry eye symptoms [19, 20].

The viscosity-enhancing agents used in tear supplement formulations include hyaluronic acid (HA), also termed hyaluron and sodium hyaluronate, [13]. Hyaluronic acid is a naturally occurring anionic, non-sulfated glycosaminoglycan that is distributed widely throughout connective, epithelial, and neural tissues. It can be very large, with its molecular weight often reaching several million Daltons. Hyaluronic acid is an important component of articular cartilage and is found in abundance in the synovial fluid around joints, and in the vitreous and aqueous humour [21]. A number of studies have demonstrated its ability to bind to ocular surface cells and its potential wound-healing properties [22]. Hyaluronic acid is used in a variety of tear supplements to increase viscosity and provide enhanced lubrication. Very high-viscosity eye drops are typically recommended for overnight use, with low-viscosity drops being used in the daytime. Studies using hypotonic hyaluronic acid-based ocular lubricants demonstrated an improvement in both symptoms and various signs of DED [23, 24]. However, more studies linking the ability of lubricants to reduce tear film osmolarity and their impact on DED symptoms and signs are warranted. There are a number of studies demonstrating that osmoprotectants have a beneficial effect on the treatment of DED. The osmoprotective effect of osmoprotectants may function better with different pharmaceutical kinetics than with individual osmoprotectants. Trehalose is a naturally occurring disaccharide, present in numerous non-mammalian species, which allows cells to survive in unfavorable environments. A new eye drop formulation that contains both HA and trehalose has been developed to capitalize on the lubricant properties of HA and bioprotectant properties of trehalose [25].

Pantothenic acid, also known as vitamin B5, is a water-soluble vitamin that is naturally present in some foods (i.e., eggs, milk, vegetables, beef, chicken, and whole grains), added to others, and available as a dietary supplement. Scientists are studying pantothenic acid or vitamin B5 to understand how it affects health. The results of this research are briefly summarized below. The application of 2% dexpanthenol drops on corneal epithelial wounds after surface laser ablation only induced little effect on corneal epithelial regeneration, and, in general, the effect was of minimal clinical relevance after 2 months of use [27]. Dexpanthenol has
been found to be effective in the treatment of dry eye, where it exerted superior improvement in disturbances of corneal epithelium permeability compared with dexamethasone-free drops [28].

The presence of oxygen-free radicals in the tears of patients with DED has resulted in the exploration of the potential application of antioxidants for the management of DED. A study using stratified human corneal limbal epithelial cells showed that several antioxidants may be beneficial if incorporated into topical ocular lubricants. The bioavailability and efficacy of antioxidants in human corneal limbal epithelial cells were measured to determine whether antioxidants might be beneficial constituents of lubricant eye drops. It was found that the antioxidants were effective at quenching reactive oxygen species in human corneal limbal epithelial cells, indicating that they are bioavailable and might be effective in protecting the corneal epithelium from oxidative damage if included in a lubricant eye drop [26].

Treatment of DED is based on etiology and severity. The ultimate goal for management circles back to the new definition: to restore homeostasis of the ocular surface. The treatment algorithm, however, is not rigid—DED is too diverse. The heterogeneity of the DED patient population mandates that patients be managed and treated based on individual profiles, characteristics, and responses [16].

A new drug against DED – eye drops under the brand name Regenopia (Trehalose 3% with hyaluronic acid 0.15% and dexamethasone 2%) have appeared in the Georgian pharmaceutical market. We decided to investigate the efficiency of Regenopia in the treatment of moderate and severe degree dry eye in order to put it in our scheme of treatment of DED.

Clinical observation on the use of Regenopia eye drops in DED was conducted from February 1 to May 30, 2023. 128 patients were selected for further observation (256 eyes). There were 43 men and 85 women, whose ages ranged from 18 to 60 years. 75% of patients (192 eyes) had moderate dry eye, 25% (64 eyes) had severe dry eye, of which 24 eyes were diagnosed with superficial punctate keratitis.

Patients with chronic and autoimmune diseases were excluded from the study.

**METHODS:**

Clinical diagnosis of DED was confirmed by the following methods:

**Anamnoses** – included the following questions:
- Eye discomfort in connection with environmental conditions
- Frequent blinking of the eyes
- Redness of the eye mucosa
- Sensation of pain, burning, stinging in the eyes
- Feeling of heaviness, fatigue, dryness in the eyes
- Feeling of a foreign body (sand) in the eye
- Visual discomfort - periodic deterioration and blurring of vision
- Fear of light
- Tearing, discharge from the eyes

**Instrumental Methods:**
- Visometry/biomicroscopy,
- Determination of tear production ability by Schirmer test,
- Determination of tear film stability according to the tear film break-up time (TBUT).
Before starting the treatment, the majority of patients reported discomfort in connection with environmental conditions. 89 out of 128 patients (69.5%) mentioned discomfort related to the cold, wind, sun, etc. 42 (32.8%) patients complained of increased frequency of eye blinking, 94 (73.4%) patients complained of eye redness, 78 (60.9%) patients reported pain, burning and stinging in the eyes and 72 (56.3%) patients complained of feeling of heaviness, fatigue and dryness in the eyes. 63 (49.2%) patients had the feeling of a foreign body (sand) in the eyes. 75 (58.6%) patients complained of visual discomfort, periodic deterioration of vision, blurring. 48 (37.5%) patients reported fear of light. 45 (35.2%) patients complained of tearing and sticky discharge from the eyes. Schirmer’s test improved to 7-8 mm in 42.2% (108 eyes), TBUT increased to 15 seconds in 38.3% (98 eyes). Superficial keratitis remained in 11 (45.8%) patients.

Six weeks after the start of treatment: 14 (10.9%) patients had discomfort related to environmental conditions, 5 (3.9%) patients – increased frequency of eye blinking, 8 (6.3%) patients - redness of the eye mucosa, 3 (2.3%) patients - pain, burning and stinging sensations in the eyes. 5 (3.9%) patients - the feeling of heaviness, fatigue and dryness in the eyes. The sensation of a foreign body (sand) in the eyes relieved in all patients, visual discomfort, periodic deterioration of vision, blur remained in 4 (3.1%) patients, fear of light disappeared in all patients, tearing remained in 2 (1.6%) patients. The Schirmer test value was greater than 10 mm in 82.8% (212 eyes). TBUT was more than 15 seconds in 89.1% (228 eyes). None of the patients had superficial punctate keratitis six weeks after the start of treatment.

Regenopia eye drops alleviate the symptoms of moderate and severe dry eye syndrome. Additionally, it provides a feeling of long-lasting comfort. The bioprotective, osmoprotective, regenerative properties of trehalose significantly enhance hyaluronic acid’s ability to provide effective hydration and long-term symptom relief along with the regenerative action of dexamethasol. Sodium hyaluronate moisturizes, and thanks to its mucoadhesive properties, it ensures better adherence of the preparation to the eye surface. It also

**Instrumental methods** - Visometry/biodynamics, Schirmer test, Tear Break Up Time Test.

Three weeks after the start of treatment: 53 (41.4%) patients reported discomfort related to environmental conditions, 28 (21.9%) patients – increased frequency of eye blinking, 52 (40.6%) patients - redness of the eye mucosa, 44 (34.4%) patients - pain, burning and stinging sensations in the eyes, 35 (27.3%) patients - the feeling of heaviness, fatigue and dryness in the eyes, 28 (21.9%) patients - feeling of a foreign body (sand) in the eyes, 37 (28.9%) patients - visual discomfort, periodic deterioration of vision, blurring, 22 (17.2%) patients - fear of light, 25 (19.5%) patients - tearing and sticky discharge from the eyes. Schirmer’s test improved to 7-8 mm in 42.2% (108 eyes), TBUT increased to 15 seconds in 38.3% (98 eyes). Superficial keratitis remained in 11 (45.8%) patients.
supports the stability of the tear film. D-panthenol improves hydration and helps to regenerate the protective barrier of the eye. Regenopia significantly reduces the intensity of symptoms and increases the patient’s quality of life, which allows us to recommend Regenopia as an effective, safe, and reliable treatment for moderate to severe dry eye disease.

The research was conducted with the support of the Pharmaceutical Company Rich Group LLC, which represents the official distributor of Regenopia Eye Drops in Georgia.

References


РЕЗЮМЕ

Регенопия — многообещающее новое средство для лечения заболеваний сухого глаза

Шенгелая ТТ, Папава МВ, Джоджуа ТДж

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Цель — исследование результатов использования глазных капель Регенопия для лечения синдрома сухого глаза (ССГ). С 1 февраля по 30 мая 2023 года проводили лечение 128 пациентов с ССГ (256 глаз) в возрасте от 18 до 60 лет (из них 85 жен. и 43 муж.) глазными каплями Регенопия. Диагноз ССГ был поставлен на основании анамнеза, инструментальных и клинических методов исследования. ССГ средней степени выявлена у 75% (192 глаза), тяжёлая степень — у 25% (64 глаза). В результате исследования эпителиального слоя роговицы и конъюнктивы в 24 глазах был выявлен поверхностный точечный кератит. Пациентам закапывали по одной капле Регенопии 3 раза в день в оба глаза (в случаях поверхностного точечного кератита назначался комплексный метод лечения). Через 3 и 6 недель после начала лечения проводилось повторное исследование пациентов. В результате исследования было установлено, что биозащитные, осмозащитные и регенеративные свойства трегалозы значительно усиливают способность гиалуроновой кислоты обеспечивать эффективное увлажнение и долгосрочное облегчение симптомов. Применение Регенопии значительно снизило интенсивность симптомов, повысило трудоспособность пациентов и улучшило качество жизни, что позволяет нам рекомендовать Регенопию в качестве эффективного, безопасного и надежного средства для лечения сухости глаз средней и тяжелой степени.

Ключевые слова: Регенопия, синдром сухого глаза, лечение, sodium hyaluronate, trehalose, and D-panthenol
Regenopia

Sodium Hyaluronate
Trehalose
D-Panthenol

- Innovative
- Natural
- Safe (Preservative-free)
- Contact lens friendly

A unique complex of Trehalose, Hyaluronic Acid and D-Panthenol ensures the ability of the medication to reduce tear osmolality, rapidly restore the damaged surface of the eye, maintain its healthy homeostasis and bring immediate relief to eyes.
რეზულტატები

რეგენოპია - სასამართლო მოქმედებები მოშრალი თვითოვანი


tinatin t. shengelaia, medea v. papava, tea j. jojua