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Research Article

A New Approach to Ocular Surface Disease Treatment

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ABSTRACT

The purpose of this study is to develop an algorithm for Chronic Corneal Dystrophic Disease treatment using 1% sodium hyaluronate in the complex treatment as well as updating drug information in the treatment of corneal dystrophy. The efficiency of eye surface disease treatment by subconjunctival injection of 1% sodium hyaluronate is studied. The study describes hyaluronic acid functions depending on its molecular weight. It shows the necessity of using sodium hyaluronate of low molecular weight (500-700 kDa) in the treatment of patients with eye surface disease after keratitis. The study includes 40 patients aged 21 to 82 years. Patients had ocular surface disease in the outcome of inflammatory diseases accompanied by dry eye disease of varying severity for 2-10 years. The result shows that injections of exogenous HA during keratopathies treatment may contribute to the regeneration and activation of metabolic processes in the tissues of the cornea.

Keywords: Hyaluronic acid; Dry eye disease; Regeneration; Corneal dystrophy

INTRODUCTION

Chronic Corneal Dystrophic Disease (CCDD) is a group of diseases characterized by metabolic disorders in the cornea, leading to a decrease in its transparency. Primary dystrophies are quite rare and genetically determined. Secondary dystrophies occur as the outcome of various conditions: bacterial and viral keratitis, after surgical interventions, during the use of eye drops with preservatives. The clouding of the cornea leads to a deterioration in visual function. Another symptom that reduces the quality of life for patients with CCDD (photophobia, lacrimation, foreign body sensation, rapid fatigue of vision) is the manifestation of dry eye disease (DED). This condition not only aggravates the course of the CCDD but may also cause it. In 2017, the report from the Dry Eye Workshop II (DEWS II) at the International Conference on Dry Eye, formulated a new definition of Dry Eye Disease (DED). Today, DED is considered to be a multifactorial disease, characterized by a violation of the tear film homeostasis and accompanied by ocular symptoms, in which the instability and hyperosmolarity of the tear film, inflammation, and damage to the surface of the eye, as well as sensorineural disorders, play the etiological role [1]. In the complex treatment of DED, hyaluronic acid (HA) in drops has long been used. However, HA often turns out to be insufficiently effective, even in simple conditions, i.e., after keratorefractive operations. A randomized, double-blind, placebo-controlled study demonstrated that an increase in the thickness of the tear film caused by the use of HA in drops was observed within only 30 minutes in healthy people [2]. In this regard, the subconjunctival administration of the HA drug for the treatment of grade III-IV DED seems to be promising.

Functions of HA fragments depending on their molecular weight

it is known that different HA fractions mediate different effects. HMW-HA high molecular weight hyaluronan (> 1000 kDa) (kDa: An atomic mass unit equal to 1,000 daltons; usually used to describe the molecular weight of large molecules such as proteins), Oligo-HA (1000 kDa). This molecule occupies a significant part of the extracellular space and is capable of not only retaining a large amount of water, providing mechanical properties of tissues, but also performing the function of a molecular "sieve", protecting cells from the pathological effects of microorganisms, cytokines, and ions. The protective effects of HMW - HA may be related to its ability to suppress inflammation. Oligo-HA (<10kDa). A large number of effects of Oligo-GA are mediated by its interactions with receptors of

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immunocompetent cells, realized in the potentiation of inflammation. Oligo-HA also affects endotheliocytes. Oligomers consisting of 6, 8 or 10 disaccharide elements potentiate endothelial cell proliferation and VEGF secretion [3].

MMW - medium molecular weight hyaluronan 250-1000 kDa, and LMW-HA low molecular weight hyaluronan (10-250 kDa). Fragments of medium and low molecular weight are often detected as a polydisperse fraction of molecules with overlapping molecular weights. MMW- and LMW-HA exhibit the properties of both HMW and Oligo-HA. It is reported that MMW-HA can induce the differentiation of mesenchymal cells (chondrocytes, keratinocytes, fibroblasts, including the induction of expression of growth factors; endotheliocytes), mediating a normal response to damage [4]. LMW-HA accelerates wound healing by inducing the expression of CD44, RHAMM and the accumulation of type 3 collagen. Interacting with TLR4, LMW-HA induces neutrophil apoptosis, limiting the inflammatory response [5]

Materials and Methods

The study included 40 patients (51 eyes) aged 21 to 82 years. These were patients with ocular surface disease in the outcome of inflammatory diseases accompanied by DED of varying severity for 2-10 years. Before inclusion in the study, all of them were regularly observed by an ophthalmologist and received adequate tear replacement therapy with drops containing HA. Each patient included in the study filled out a questionnaire and informed consent. All patients underwent complex ophthalmological examination, including visometry, pneumotonometry, biomicroscopy, keratopachymetry, optical coherence tomography (OCT) of the anterior segment of the eye. Diagnosis of BSH was mandatory, including the Schirmer test, the time of tear film break down, the meibomian glands examination, LIPCOF test, and fluorescein staining. In the presence of indications, keratoplasty was performed. Man-Whitney test was used to verify the reliability of group differences, and one-way analysis of variance (ANOVA) was used to establish the relationship between the parameters. Statistical data processing was carried out in the application package Statistica 8.0.

Clinical findings

Despite the use of HA installations, no improvement was observed, which was the reason for the inclusion in this study. 28 patients underwent complex therapy with the inclusion of an injectable form of hyaluronic acid 1%. 20 patients (24 eyes) were included at the early stages after stopping the acute inflammatory process (after one or two months). As a result, positive clinical outcomes were obtained: increased visual acuity, corneal transparency, eliminating the corneal syndrome, restoring the corneal thickness in pathological focuses, improving the condition of the tear film - increasing the total tear production and improving the quality of the tear film. 8 patients (8 eyes) were included in the study after a long period of relief from inflammation (6 months or more). In this group of patients, clinical outcomes during therapy were not so pronounced. Only three patients had increased visual acuity. Normalization of the corneal thickness, improvement in tear production and quality of the tear film were observed in all patients. The absence of an increase in visual acuity is explained by the central localization of opacities. Changes in objective indicators of the ocular surface state (time of the tear film break down, Schirmer test, LIPCOF test, biomicroscopy data) were characterized by positive dynamics during therapy (Figures 1 and 2). Schirmer's test and tear film break downtime were changed most quickly and significantly, which indicates the beneficial effect of therapy on both the aqueous and mucin layers of the tear film. In young patients with short dry eye experience, positive dynamics were also observed according to the results of the LIPCOF test. It is worth noting that in elderly patients, this test was not informative.

Figure 1: Shirmer test changes during treatment in patients with keratopathy after keratitis. 0) state before therapy, 1) after the first injection, 2) after the second injection, k1) after the third injection, k2) control one month after the last injection.

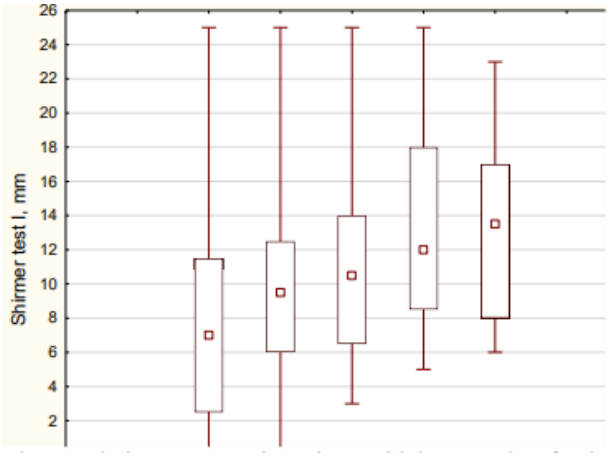
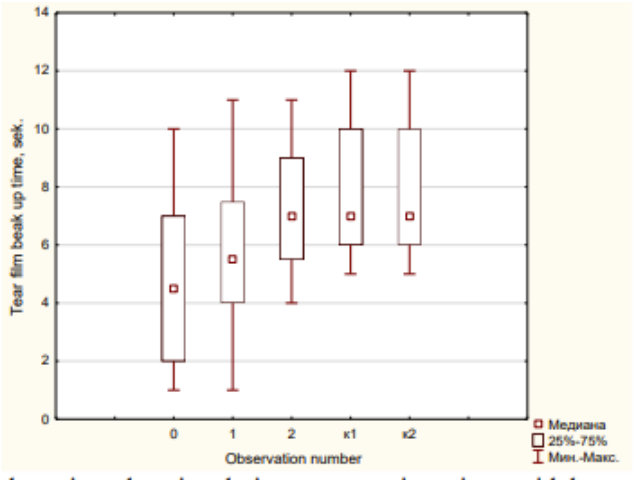


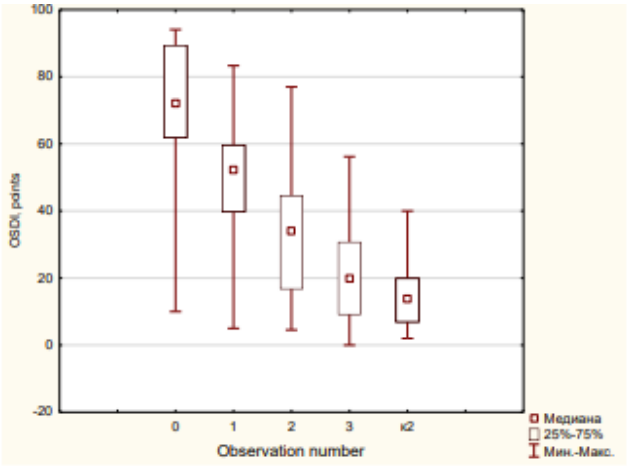
Figure 2: Tear film break up time changing during treatment in patients with keratopathy after keratitis. 0) state before therapy, 1) after the first injection, 2) after the second injection, k1)after the third injection, k2)control one month after the last injection.



In the outcome of the inflammatory process, corneal tissue densification was formed, accompanied by edema. According to pachymetry, the thickness of the cornea both in the damage zone and outside it decreased after a course of therapy. The assessment of the effect of DED therapy is mostly based on the

subjective feelings of patients. A decrease in the OSDI index was noted already after the first injection Медиана 25%-75% Мин.-Макс. 0 1 2 к1 к2 Observation number 0 2 4 6 8 10 12 14 Tear film beak up time, sek. and continued to decrease progressively during the course and after its completion until the control, one month after the last injection (Figure 3).

Figure 3: Ocular surface disease index changing during treatment in patients with keratopathy after keratitis. 0) state before the start of therapy, 1)after the first injection, 2)after the second injection, k1) after the third injection, k2) control one month after the last injection.



12 patients of this group had gross vascularized opacities in the outcome of severe inflammatory processes (corneal ulcers, perforation of the cornea severe long-term treated keratitis). Everyone underwent subtotal keratoplasty with a donor cornea according to a standard technique. 8 patients underwent preoperative preparation with the introduction of hyaluronic acid 1 time per week No. 4. In these patients, rapid epithelization was observed on the 3rd day after keratoplasty (Figure 4, 5).

Figure 4: Biomicroscopy of the anterior segment of patient G. before surgical treatment.

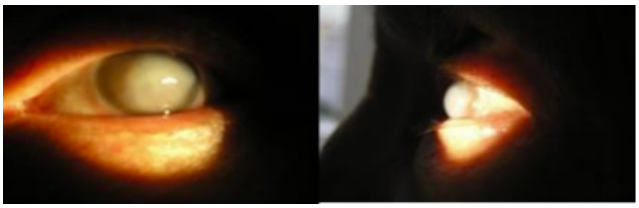


Figure 5: Biomicroscopy of the anterior segment of patient G. after surgical treatment.

Four patients did not have preoperative preparation. In the postoperative period, delayed epithelization was observed (absent on day 3), which was an indication for the introduction of HA. After subconjunctival administration of 1% hyaluronic acid once a week No. 4, epithelization was completed already on the 10th day in one patient, on the 12th day in another patient. The algorithm for treating patients with CCDD in the outcome of inflammatory diseases of the Медиана 25%-75% Мин.-Макс. 0 1 2 3 к2 Observation number -20 0 20 40 60 80 100 OSDI, points anterior segment includes subconjunctival administration of 1% injectable hyaluronic acid 0.5 ml once a week No. 3. Then, for most patients with DED I-II, a transfer to the instillation of drugs with hyaluronic acid is indicated. For patients with DED III-IV, hyaluronic acid injection is indicated once a month with the monitoring of the eye anterior segment state. In the presence of severe xerosis (Sjögren's syndrome or neurotrophic disturbances), the injection of 1% hyaluronic acid 1.0 ml under the skin of the eyelids and subconjunctival 0.5 ml is indicated to improve the regenerative processes of orbit tissue.

CONCLUSION

Injections of exogenous HA during keratopathies treatment may contribute to the regeneration and activation of metabolic processes in the tissues of the cornea. In this case, it seems most justified to use a low- and medium-molecular fraction of HA, combining the protective functions of high-molecular hyaluronan and the activating effect of Oligo-HA. An additional favorable consequence of the exogenous HA injections is the activation of endogenous HA synthesis, which in turn helps restore homeostasis of the anterior segment of the eye for a long time after a course of therapy.

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