Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 8 Issue 4 April 2025

Research Article

Efficiency of 0.01% Dexamethasone Solution in Comprehensive Therapy of Dry Eye Disease

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Received: March 12, 2025

Published: March 24, 2025

Abstract

Introduction: Anti-inflammatory therapy of patients with dry eye disease is based today mainly on glucocorticoids' instillations. In spite of the fact that dexamethasone in official dosage (0.1%) has a marked local anti-inflammatory effect, its broad use is limited by the presence of a destructive process in the cornea. Taking this into account, the authors developed a drug containing 0.01% dexamethasone phosphate in combination with 6% polyvinylpyrolidone and 1.5-5.5% dextrose solution.

Objective: Study the impact of the developed medication on the inflammatory process dynamics in the tissues of the ocular surface in patients with dry eye disease of various ethiology.

Materials and Methods: The material of this study was based on the results of examination and treatment of 25 volunteers (50 eyes) with corneal-conjunctival xerosis developed on the background of 7 cases of meibomian blepharitis (14 eyes), 8 cases of perimenopause (16 eyes), and 10 cases of Sjögren's syndrome (20 eyes).

All patients used the developed medication in the form of eyedrops 3-4 times daily on the background of tear replacement therapy. Prior to therapy and on day 28 of the study the following parameters were assessed, inferior tear meniscus index, precorneal tear film production, stability and osmolarity, staining of ocular surface epithelium with fluorescein sodium solution, as well as bengal rose and lissamine green. Cytokines' levels were determined in the tear fluid and blood plasma with the help of ELISA test: interleukins-1β, 2, 4, 6, 8, 10, 17A, interleukin receptor antagonist 1, tumour necrosis factor α, interferons α and γ. Besides, all the subjects were asked to fill in a questionnaire to evaluate subjective signs of the ocular surface epithelium xerosis or Ocular Surface Disease Index (OSDI).

Results: By day 28 of the study statistically significant increase of the tear meniscus index, precorneal tear film stability, main and total tear production and decrease of tear film osmolarity were observed. Besides, the staining degree of the ocular surface epithelium with bengal rose and lissamine green (van Bijsterveld score) and with fluorescein sodium (Oxford score) decreased. Also, the positive dynamics of the objective parameters of the ocular surface epithelium was confirmed by the subjects' subjective evaluation of their quality of life.

Conclusion: The results of the study performed prove the high clinical efficiency of the developed medication that has a marked local anti-inflammatory effect in the therapy of dry eye disease of various ethiology.

Keywords: Anti-inflammatory Therapy; Dry Eye Syndrome; Cytokines' Levels in the Tear Fluid

Introduction

For many years, the dry eye disease (DED) occupies an important place in the structure of opthalmologic pathologies. On the one hand, this is connected with wide prevalence of the disease under consideration, on the other hand, with the severity of the clinical course and outcomes of some of its clinical forms [1].

At that, DED clinical manifestations, viz. the development of the so called corneal-conjunctival xerosis, are often followed by irreversible morphological changes of the conjunctiva, mainly the cornea. And, as demonstrated by the practice, those may be seen in a wide range: from minimal dystrophic changes of the epithelium to deep destructive process, progressive corneal ulcer or even keratomalacia [1,2].

As known, the central link of DED pathogenesis is the precorneal tear film stability violation followed by the increase of its evapouration, and osmolarity, and as the result, development of inflammatory processes in the ocular surface tissues [1]. Hence, the important vector of pathogenetically oriented DED therapy is the use of anti-inflammatory medications.

Traditionally, anti-inflammatory therapy is based on the use of glucocorticoids, in particular, dexamethasone phosphate. This is connected with the fact that the latter blocks such transcription factors as nuclear factor kβ (NF-kβ) and protein activator 1 (AP-1), thus repressing DNA binding and inhibiting further transcription of IL-2 key cytokine that regulates cellular immune response. Besides, under the impact of dexamethasone phosphate the number of T-cells decreases, as well as their influence on B-cells, the production of immunoglobulins slows down, while the formation of the components of the complement system goes down and their degradation goes up.

However, long-term use of dexamethasone phosphate in official dosage (0.1%) is limited by a wide range of its side effects: IOP increase, development of steroid cataract and glaucoma, thinning of xerotically changed cornea, that lead to progression of the ulcerative process and development of corresponding complications. Taking this into account, the authors developed a drug containing 0.01% dexamethasone phosphate in combination with 6% polyvinylpyrolidone and 1.5-5.5% dextrose solution [4].

As is commonly known, polyvinylpyrolidone is the polimer base of many modern "artificial tear" preparations, since it stimulates endogenous interferon generation, increases the wettability of the hydrofobic corneal epithelium and conjunctiva and improves tolerability of pharmacologically active drugs when used as drops into conjunctiva cavity. The addition of dextrose solution is substantiated by its property to stabilise cellular membranes of the ocular surface epithelium.

This study delved into the efficiency of the use of the medication on offer in comprehensive therapy of patients with main pathogenetic types of corneal-conjunctival xerosis.

Objective

Study the impact of the developed medication on the inflammatory process dynamics in the tissues of the eye surface in patients with dry eye disease of various ethiology.

Materials and Methods

The material of the study comprises of the results of examination and therapy of 25 volunteers (50 eyes): 6 males (24%) and 19 females (76%) at the age from 40 to 80 years (on average, 60.44 ± 11.1 yrs) with dry eye syndrome of various ethiology: 7(14 eyes) - due to meibomian blepharitis, 8(16) - perimenopause, and 10(20) - Sjögren's syndrome.

It is known, that most important in DED pathogenesis in case of meibomian blepharitis is precorneal tear film stability violation, in case of perimenopause - tear film lipids and mucins production drop down, and in case of Sjögren's syndrome - the simultaneous decrease of secretion of all components of precorneal tear film. Thus, the subjects included patients with all the main pathogenetic DED types.

Control group amounted of 25 volunteers (50 eyes): 5 males (20%) and 20 females (80%) at the age from 37 to 78 years (on average, 62.5 ± 10.9 yrs) with DED of the same ethiology: 6 subjects (12 eyes) with DED due to meibomian blepharitis, 9 (18) - due to perimenopause, and 10(20) - due to Sjögren's syndrome.

All subjects from both groups received instillations into conjunctival cavity with preservative-free tear replacement agent on the basis of polyvinylpyrolidone and polyvinyl alcohol - Ophtholique BK (Sentiss, Pvt. Ltd., India), on average, 3-4 times daily, and the subjects from the main group received also the medication developed by the authors, 2-3 times daily.

Comprehensive examination was carried out prior to the study and on day 28. In particular, subjective signs of epithelium xerosis were assessed with the help of the Ocular Surface Disease Index (OSDI) [5]. Functional examination included evaluation of the inferior tear meniscus index, precorneal tear film stability according to M.S. Norn (1969), pronouncement of the bulbar conjunctiva fold at the eyelid free margin according to H. Hoh (2006) technique, measuring the main and total tear production values according to L. Jones (1966) and O. Schirmer (1903), as well as assessing in the course of ocular surface biomicroscopy the degree of its staining with bengal rose and lissamine green solutions using the 4-point van Bijsterveld score, and with fluoroscein sodium using the Oxford score [6-11]. In order to increase the accuracy and comparability of the study results, the authors limited themselves to quantitative assessment of staining degree of cornea only.

Besides that, osmolarity of precorneal tear film was measured in all the subjects with TearLab Osmolarity System device (TearLabCorp., USA). Then cytokines' levels were measured in the tear fluid with the help of ELISA test: interleukins1β, 2, 4, 6, 8, 10, 17A, interleukin receptor antagonist 1, tumour necrosis factor α, interferons α and γ (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17A, IL-1Ra, TNF-α, INF-α, INF-γ, respectively). To carry out lab tests, 0.5ml of tear fluid was needed. Provided that usually one cannot get sufficient tear fluid from DED patients, the authors used the following technique.

After local epibulbar anaesthesia with 0.4% oxybuprocaine solution (Inocaine, Sentiss, Pvt. Ltd., India) 1.0ml of 0.9% sodium chloride was instilled drop by drop into conjunctival cavity with the help of insulin syringe (without a needle) and immediately lavage fluid was collected with disposable pipette into sterile and labelled eppendorf. In the result of these manipulations, 0.5ml of tear fluid was collected in eppendorf ("diluted" in standard amount of isotonic sodium chloride) [12]. The tear fluid from the conjunctival cavity of the second eye was collected in a similar way. Prior to lab tests stage, the material thus collected was stored in the freezer at -60.0°C.

In recent years, thanks to intensive studies of lymphoid tissue associated with mucous membranes (Mucosa-associated lymphoid tissue, MALT), it became evident that it is involved in all the processes that take place in mucous membranes, physiological, as well as pathological, including inflammatory ones. It includes all the systems having the epithelium: lymphoid tissue associated with gastrointestinal and urogenital tracts, bronchi, as well as the ocular surface. Eye-associated lymphoid tissue (EALT) is represented by lymphoid tissue associated with lacrimal gland, conjunctiva, and lacrimal passages. It belongs to peripheral parts of the immune system organs and is closely connected with it by way of blood-ocular barrier [13-15]. Due to this very reason, the authors defined the levels of cytokines in blood plasma as well using ELISA test.

Results Obtained and Discussion

The dynamics of the clinical and physiological signs of the corneal-conjunctival xerosis in patients with DED of various pathogenetic types in both groups under comparison is given in Tables 1-3.

In DED patients on the background of meibomian blepharitis (see Table 1) on day 28 of therapy with medication containing 0.01% dexamethasone phosphate in combination with 6% polyvinylpyrolidone and 1.5-5.5% dextrose pronouncement of ocular surface xerosis subjective signs decreased with statistical significance ($p < 0.001$). At the same time, statistically significant increase of the tear meniscus index and total tear production were found ($p < 0.01$), as well as the decrease of the degree of staining of conjunctival and corneal epithelium with bengal rose, lissamine green and fluorescein sodium solutions ($p < 0.05$-0.001). Besides, subjects from this group while receiving the medication under study demonstrated significant decrease of precorneal tear film osmolarity ($p < 0.05$). It should be mentioned, that the pronouncement of bulbar conjunctiva fold at the eyelid free margin and total tear production were statistically insignificant on the background of the performed therapy ($p > 0.05$).

In the control group, on day 28 the authors also found statistically significant decrease of the intensity of ocular surface epithe-

Evaluated parameter	Observational stages (days)							
	Main group (n = 14)				Control group (n = 12)			
	Initial data	Day 28 of therapy	t	p	Initial data	Day 28 of therapy	t	p
Ocular surface disease index	84.52 ± 4.96	30.05 ± 5.08	18.8	<0.001	73.61 ± 4.91	37.15 ± 4.72	12.0	<0.001
Osmolarity, mOsm/l	320.86 ± 11.39	293.86 ± 13.25	5.6	< 0.05	323.83 ± 8.73	302.58 ± 10.02	5.3	>0.05
Tear meniscus index	1.07 ± 0.25	2.28 ± 0.45	8.7	< 0.01	0.91 ± 0.25	1.41 ± 0.49	2.4	>0.05
Pronouncement of the bulbar conjunctiva fold at the eyelid free margin	1.78 ± 0.67	0.57 ± 0.62	4.9	>0.05	1.83 ± 0.55	0.91 ± 0.49	4.1	>0.05
Precorneal tear film stability, s	5.43 ± 1.65	9.28 ± 0.72	7.7	< 0.05	5.09 ± 0.49	8.71 ± 0.61	15.7	<0.05
Main tear production, mm/5 min	2.03 ± 0.81	3.54 ± 0.70	5.2	>0.05	2.64 ± 0.36	4.47 ± 0.69	8.0	<0.05
Total tear production, mm/5 min	4.43 ± 1.14	9.60 ± 1.71	9.1	<0.01	7.74 ± 0.56	8.76 ± 0.21	5.7	>0.05
Epithelium assessment by van Bijsterveld score using rose bengal solution, points	4.64 ± 0.61	1.14 ± 0.63	14.6	<0.001	4.58 ± 0.49	2.58 ± 0.40	9.5	<0.01
Epithelium assessment by van Bijsterveld score using lissamine green solution, points	4.50 ± 0.98	1.42 ± 0.49	10.2	<0.001	4.75 ± 0.72	2.41 ± 0.41	9.0	<0.01
Epithelium assessment by Oxford score using fluorescein sodium solution, points	3.07 ± 0.70	0.64 ± 0.48	10.6	<0.05	2.33 ± 0.47	1.75 ± 0.43	3.1	>0.05

* Ratio between the tear meniscus height and base - tear meniscus index value: 1 (decrease of moisture amount in the conjunctiva cavity); 2 (normal moisture amount); 3 (increase of moisture amount) (L.P. Prozornaya, V.V. Brzheskiy, 2006);

**0 - no staining; 1 - weak; 2 - moderate; 3 - diffuse staining;

***0 - no staining; 1 - minimal; 2 - weak; 3 - moderate; 4 - diffuse; 5 - total.

Table 1: The dynamics of clinical and functional DED parameters in patients with meibomian blepharitis on the background of the performed therapy.

Evaluated parameter	Observational stages (days)							
	Main group (n = 14)				Control group (n = 12)			
	Initial data	Day 28 of therapy	t	p	Initial data	Day 28 of therapy	t	p
Ocular surface disease index	75,51 ± 5,29	25,51 ± 4,51	19,1	<0,001	77,77 ± 3,40	42,59 ± 4,51	17,7	<0,01
Osmolarity, mOsm/l	315,06 ± 13,41	301,81 ± 11,27	2,9	>0,05	328,44 ± 12,44	309,11 ± 6,72	5,7	>0,05
Tear meniscus index	0,81 ± 0,39	2,06 ± 0,65	6,6	< 0,05	0,94 ± 0,53	1,66 ± 0,47	4,3	>0,05
Pronouncement of the bulbar conjunctiva fold at the eyelid free margin	1,87 ± 0,78	0,50 ± 0,50	6,0	>0,05	2,00 ± 0,66	1,05 ± 0,52	4,7	>0,05
Precorneal tear film stability, s	5,79 ± 1,20	10,34 ± 0,96	11,7	< 0,01	4,72 ± 0,83	8,73 ± 1,12	12,2	<0,01
Main tear production, mm/5 min	1,99 ± 0,67	4,50 ± 0,48	12,0	<0,001	2,27 ± 0,75	4,83 ± 0,53	11,6	<0,01
Total tear production, mm/5 min	5,20 ± 1,05	9,50 ± 1,13	11,1	<0,01	7,71 ± 0,33	9,12 ± 0,39	11,8	<0,01
Epithelium assessment by van Bijsterveld score using rose bengal solution, points	4,43 ± 0,99	1,37 ± 0,69	9,9	<0,001	5,16 ± 0,50	2,44 ± 0,49	16,1	<0,001
Epithelium assessment by van Bijsterveld score using lissamine green solution, points	4,56 ± 1,41	1,75 ± 0,83	6,7	<0,001	5,05 ± 0,52	2,94 ± 0,52	12,5	<0,001
Epithelium assessment by Oxford score using fluorescein sodium solution, points	3,06 ± 0,74	0,56 ± 0,49	10,9	<0,01	2,66 ± 0,57	1,61 ± 0,48	5,9	>0,05

* Ratio between the tear meniscus height and base - tear meniscus index value: 1 (decrease of moisture amount in the conjunctiva cavity); 2 (normal moisture amount); 3 (increase of moisture amount) (L.P. Prozornaya, V.V. Brzheskiy, 2006);

**0 - no staining; 1 - weak; 2 - moderate; 3 - diffuse staining;

***0 - no staining; 1 - minimal; 2 - weak; 3 - moderate; 4 - diffuse; 5 - total.

Table 2: The dynamics of clinical and functional DED parameters in perimenopausal females on the background of the performed therapy.

Evaluated parameter	Observational stages (days)							
	Main group (n = 14)				Control group (n = 12)			
	Initial data	Day 28 of therapy	t	p	Initial data	Day 28 of therapy	t	p
Ocular surface disease index	74,17 ± 6,79	23,75 ± 5,60	17,2	<0,001	82,08 ± 4,85	44,58 ± 3,86	18,2	<0,01
Osmolarity, mOsm/l	342,40 ± 12,11	316,95 ± 6,82	8,0	< 0,05	340,60 ± 11,76	321,85 ± 6,10	6,2	>0,05
Tear meniscus index	0,20 ± 0,40	0,85 ± 0,57	4,1	>0,05	0,45 ± 0,49	0,80 ± 0,50	2,2	>0,05
Pronouncement of the bulbar conjunctiva fold at the eyelid free margin	1,90 ± 0,63	0,40 ± 0,58	7,9	< 0,05	2,15 ± 0,48	0,85 ± 0,36	5,9	>0,05
Precorneal tear film stability, s	5,86 ± 1,34	9,57 ± 1,20	9,0	< 0,05	4,96 ± 0,69	8,07 ± 1,22	9,7	<0,05
Main tear production, mm/5 min	2,01 ± 0,64	4,11 ± 0,67	10,0	<0,01	1,69 ± 0,43	3,82 ± 1,01	8,6	<0,01
Total tear production, mm/5 min	5,31 ± 1,43	9,93 ± 2,10	8,0	<0,05	5,83 ± 0,50	8,60 ± 0,44	11,8	>0,05
Epithelium assessment by van Bijsterveld score using rose bengal solution, points	4,50 ± 0,50	1,70 ± 0,46	18,7	<0,001	5,30 ± 0,45	3,40 ± 0,66	10,9	<0,05
Epithelium assessment by van Bijsterveld score using lissamine green solution, points	4,65 ± 1,35	2,10 ± 0,70	7,5	<0,01	5,20 ± 0,40	3,40 ± 0,48	12,9	<0,05
Epithelium assessment by Oxford score using fluorescein sodium solution, points	3,05 ± 0,67	0,55 ± 0,58	12,5	<0,01	2,80 ± 0,50	1,85 ± 0,49	7,8	>0,05

* Ratio between the tear meniscus height and base - tear meniscus index value: 1 (decrease of moisture amount in the conjunctiva cavity); 2 (normal moisture amount); 3 (increase of moisture amount) (L.P. Prozornaya, V.V. Brzheskiy, 2006);

**0 - no staining; 1 - weak; 2 - moderate; 3 - diffuse staining;

***0 - no staining; 1 - minimal; 2 - weak; 3 - moderate; 4 - diffuse; 5 - total.

Table 3: The dynamics of clinical and functional DED parameters in patients with Sjögren's syndrome on the background of the performed therapy.

lium xerosis subjective signs ($p < 0.001$), significant increase of precorneal tear film stability, total tear production and decrease of the staining degree of ocular surface epithelium with vital staining agents ($p < 0.0\text{-}0.05$).

At the same time, the tear fluid osmolarity, tear meniscus index, pronouncement of the bulbar conjunctive fold at the eyelid free margin, total tear production and staining degree of corneal epithelium were statistically insignificant ($p > 0.05$) on the background of the performed therapy with preservative-free tear replacement agent containing polyvinylpyrolidone and polyvinyl alcohol.

Thus, patients with DED due to meibomian blepharitis demonstrated after instillations of the medication offered significant decrease of intensity of xerosis subjective signs, which is confirmed by objective research methods.

Similar dynamics of the evaluated parameters was found when treating females with DED on the background of perimenopause (see Table 2). Thus, on the background of the therapy performed by day 28 there is a significant increase of the tear meniscus index, precorneal tear film stability, as well as main and total tear production ($p < 0.05\text{-}0.001$). Besides, the degree of staining of the corneal and conjunctival epithelium with vital staining agents, as well as the intensity of the ocular surface epithelium xerosis subjective signs were significantly lower compared to initial data ($p < 0.01\text{-}0.001$). At the same time, precorneal tear film osmolarity and pronouncement of bulbar conjunctiva fold at the eyelid free margin, though had a trend to decrease, but this decrease was not statistically significant compared to the initial values ($p > 0.05$).

In the control group, the subjects showed statistically significant increase of precorneal tear film stability, tear production values, and decrease of staining degree of ocular surface epithelium

with bengal rose and lissamine green ($p < 0.01$-0.001). Objective data were followed by reduction of corneal-conjunctival xerosis subjective signs ($p < 0.01$). At the same time, precorneal tear film osmolarity, as well as tear meniscus index and pronouncement of bulbar conjunctiva fold at the eyelid free margin were statisctically insignificant compared to initial values ($p > 0.05$).

Observation results with patients having DED due to Sjögren's syndrome and receiving the study drug demonstrated a trend similar to the one described above (see Table 3). Thus, on day 28 of therapy there was a statistically significant decrease of DED objective and subjective signs intensity ($p < 0.05$-0.001). At the same time, though the values of tear meniscus index increased with the instillations of study drug, but these changes were not statistically significant compared to the initial values ($p > 0.05$).

In the control group, patients with DED due to Sjögren's syndrome demonstrated on day 28 of therapy statistically significant increase of precorneal tear film stability, decrease of staining degree of the epithelium with bengal rose and lissamine green solutions, followed by the decrease of intensity of corneal-conjunctival xerosis subjective signs ($p < 0.01$-0.05). However, tear fluid osmolarity, tear meniscus index, pronouncement of the bulbar conjunctiva fold at the eyelid free margin, as well as total tear production and staining degree of corneal epithelium with fluorescein sodium did not differ significantly from initial values ($p > 0.05$).

In order to study anti-inflammatory activity of the medication offered in patients with main pathogenetic types of corneal-conjunctival xerosis, immunological study of the cytokines' levels in tear fluid and blood plasma was performed.

The values of tear fluid immunological parameters of the patients from the main and control groups are given in Table 4.

It was found, that on the background of the therapy performed in the group of patients with DED due to meibomian blepharitis using the medication containing 0.01% dexamethasone phosphate in combination with 6% polyvinylpyrolidone and 1.5-5.5% dextrose the level of pro-inflammatory cytokines decreased. Thus, the level of IL-1β went down 1.7 times compared to initial values ($p < 0.05$), IL-2 - 2 times ($p < 0.001$), IL-6 - 1.6 times ($p < 0.05$), IL-8 - 2.4 times ($p < 0.001$), IL-1Ra - 1.5 times ($p < 0.001$), TNF-α - 1.4 times ($p < 0.01$). In spite of the decrease of pro-inflammatory cytokines IL-4 and IL-17A 1.5 and 1.1 times, respectively, in the tear fluid, the differences of these levels and initial ones were not statistically significant ($p > 0.05$). However, the level of IL-10, that has a marked immunosuppressive effect, outstandingly increased 2 times ($p < 0.05$). Production of INF-α following the performed therapy decreased 3.2 times ($p < 0.001$), which indirectly confirms activation of innate immunity. Decrease of INF-γ level was not statistically significant compared to initial levels ($p > 0.05$).

In the control group, on day 28 of therapy statistically significant decrease was found for IL-6 - 1.1 times ($p < 0.05$), IL-8 - 1.2 times ($p < 0.05$), IL-17A - 1.1 times ($p < 0.05$), IL-1Ra - 1.3 times ($p < 0.001$), TNF-α - 1.1 times ($p < 0.05$), INF-α - 1.5 times ($p < 0.05$). The changes of the levels of IL-1β, IL-2, IL-4, IL-10 and INF-γ following the therapy performed were not statistically significant against the initial levels ($p > 0.05$).

The results of tear fluid tests in patients with DED due to perimenopause showed the decrease of IL-1β 2 times ($p < 0.05$), IL-2 - 1.9 times ($p < 0.001$), IL-6 - 1.4 times ($p < 0.01$), IL-8 - 2.3 times ($p < 0.001$), IL-17A - 1.1 times ($p < 0.05$), IL-1Ra - 1.3 times ($p < 0.05$), TNF-α - 1.4 times ($p < 0.01$), INF-α - 2.7 times ($p < 0.01$). At the same time, the level of IL-10 following the therapy increased 1.7 times ($p < 0.01$), while the levels of IL-4 and INF did not change significantly ($p > 0.05$).

In the control group of patients with DED due to perimenopause statistically significant decrease was found for IL-6 - 1.2 times ($p < 0.05$), IL-8 - 1.5 times ($p < 0.01$), IL-1Ra - 1.2 times ($p < 0.05$), TNF-α - 1.3 times ($p < 0.05$), INF-α - 1.3 times ($p < 0.01$). However, the levels of IL-1β, IL-2, IL-4, IL-17A, INF-γ, as well as IL-10 following the therapy performed did not change significantly ($p > 0.05$).

The results of tear fluid tests in patients with DED due to Sjögren's syndrome following the therapy performed showed the decrease of IL-1β 2.7 times ($p < 0.01$), IL-2 - 2.4 times ($p < 0.001$), IL-6 - 1.8 times ($p < 0.01$), IL-8 - 2.9 times ($p < 0.01$), IL-17A - 1.3 times ($p < 0.05$), IL-1Ra - 1.7 times ($p < 0.05$), TNF-α - 1.5 times ($p < 0.05$), INF-α - 2.8 times ($p < 0.01$). As in previous groups, the decrease of IL-4 and INF-γ levels was not statistically significant ($p > 0.05$). At the same time, the level of IL-10 on the background of therapy increased 2 times ($p < 0.05$).

Observational stages			Evaluated parameter, pg/ml										
			IL-1β	IL-2	IL-4	IL-6	IL-8	IL-10	IL-17A	IL-1Ra	TNF-α	INF- α	INF- γ
DED due to meibomian blepharitis	Main group (n = 14)	Initial data	29,36 ± 4,15	275,78 ± 24,53	29,44 ± 3,14	39,01 ± 8,06	69,75 ± 4,11	12,00 ± 3,04	177,84 ± 9,85	338,43 ± 15,38	96,05 ± 6,75	17,37 ± 2,82	41,12 ± 12,76
		Day 28 of therapy	17,53 ± 3,89	131,81 ± 22,39	19,41 ± 4,61	24,13 ± 6,06	29,30 ± 5,52	24,96 ± 4,63	159,42 ± 20,81	229,74 ± 41,01	66,39 ± 9,15	5,47 ± 2,50	38,36 ± 10,16
		t	7,5; p < 0,05	15,6; p < 0,001	6,5; p > 0,05	4,6; p < 0,05	21,3; p < 0,001	8,5; p < 0,05	2,9; p > 0,05	9,0; p < 0,001	9,4; p < 0,01	11,4; p < 0,001	0,6; p > 0,05
	Control group (n = 12)	Initial data	24,25 ± 4,88	239,83 ± 9,32	26,66 ± 2,43	36,66 ± 3,17	63,75 ± 8,54	9,66 ± 2,11	177,91 ± 6,82	315,92 ± 4,29	98,42 ± 5,56	18,42 ± 2,89	22,16 ± 7,26
		Day 28 of therapy	19,92 ± 2,36	187,58 ± 12,24	24,50 ± 4,21	26,91 ± 2,78	42,83 ± 5,75	14,33 ± 3,88	153,33 ± 9,45	247,16 ± 10,05	70,42 ± 7,56	12,75 ± 1,74	30,25 ± 4,04
		t	2,7; p > 0,05	11,3; p > 0,05	1,5; p > 0,05	7,7; p < 0,05	6,7; p < 0,05	3,6; p > 0,05	7,0; p < 0,05	20,9; p < 0,001	9,9; p < 0,05	5,6; p < 0,05	3,2; p > 0,05
DED due to perimeno-pause	Main group (n = 16)	Initial data	21,93 ± 3,68	232,82 ± 30,28	28,41 ± 5,38	35,98 ± 6,90	70,63 ± 4,93	9,95 ± 3,19	177,58 ± 11,95	308,43 ± 24,59	85,07 ± 5,49	18,43 ± 2,98	38,37 ± 11,31
		Day 28 of therapy	11,09 ± 3,77	122,08 ± 13,47	18,73 ± 4,18	25,63 ± 4,93	30,55 ± 5,64	17,55 ± 3,59	155,02 ± 6,48	228,39 ± 29,66	59,26 ± 6,43	6,74 ± 1,34	25,51 ± 5,67
		t	8,0; p < 0,05	13; p < 0,001	5,5; p > 0,05	4,7; p < 0,01	20,8; p < 0,001	6,1; p < 0,01	6,4; p < 0,05	8,1; p < 0,05	11,8; p < 0,01	13,9; p < 0,01	4,3; p > 0,05
	Control group (n = 18)	Initial data	25,44 ± 5,42	206,05 ± 20,35	28,55 ± 3,89	38,88 ± 4,43	61,33 ± 8,01	9,50 ± 1,89	166,72 ± 10,36	314,77 ± 5,67	95,44 ± 6,37	17,55 ± 2,79	24,55 ± 8,54
		Day 28 of therapy	17,72 ± 2,99	149,27 ± 13,59	25,55 ± 3,79	27,88 ± 3,99	37,94 ± 3,49	14,61 ± 4,08	140,38 ± 13,95	248,83 ± 16,57	68,27 ± 6,43	11,72 ± 2,44	25,94 ± 7,92
		t	5,1; p > 0,05	9,6; p > 0,05	2,3; p > 0,05	7,6; p < 0,05	11,1; p < 0,01	4,5; p > 0,05	6,3; p > 0,05	15,6; p < 0,05	12,4; p < 0,05	6,5; p < 0,01	0,5; p > 0,05
DED due to Sjögren's syndrome	Main group (n = 20)	Initial data	32,08 ± 6,57	303,23 ± 33,54	27,37 ± 5,78	65,14 ± 8,57	79,73 ± 6,99	7,65 ± 1,97	225,25 ± 15.27	316,48 ± 30,55	101,54 ± 18,17	14,50 ± 3,40	33,03 ± 14,85
		Day 28 of therapy	12,37 ± 1,79	124,70 ± 25,7	21,66 ± 4,75	36,89 ± 4,77	27,23 ± 4,38	16,02 ± 3,76	171,04 ± 8,27	189,89 ± 46,34	65,05 ± 7,10	4,72 ± 2,05	26,87 ± 5,53
		t	12,6; p < 0,01	18,4; p < 0,001	3,3; p > 0,05	12,6; p < 0,01	27,7; p < 0,01	9,8; p < 0,05	7,3; p < 0.001	10,0; p < 0,05	8,2; p < 0, 05	10,7; p < 0, 01	2,3; p > 0,05
	Control group (n = 20)	Initial data	33,85 ± 5,54	305,60 ± 28,87	29,10 ± 4,84	70,10 ± 5,74	76,95 ± 4,65	10,35 ± 2,33	229,25 ± 9.74	325,20 ± 8,53	99,85 ± 7,47	17,25 ± 2,80	23,65 ± 8,55
		Day 28 of therapy	21,65 ± 2,95	198,15 ± 18,12	26,60 ± 4,94	51,85 ± 4,26	39,95 ± 3,44	14,40 ± 3,57	194,40 ± 6,06	260,30 ± 11,23	76,75 ± 6,02	11,4 ± 2,52	24,55 ± 8,63
		t	8,7; p < 0,05	13,7; p < 0,05	1,6; p > 0,05	11,1; p < 0,05	28,0; p < 0,05	4,2; p > 0,05	13,3; p > 0,05	20,1; p < 0,05	10,5; p < 0,01	6,8; p > 0,05	0,3; p > 0,05

Table 4: Dynamics of lab test values of tear fluid from patients with DED of various p n the background of performed therapy.

In the control group, following the therapy performed the tear fluid tests showed the decrease of IL-1β 1.5 times ($p < 0.05$), IL-2 - 1.5 times ($p < 0.05$), IL-6 - 1.3 times ($p < 0.05$), IL-8 - 1.4 times ($p < 0.05$), IL-1Ra - 1.2 times ($p < 0.05$), TNF-α - 1.3 times ($p < 0.01$). As in previous control groups, the decrease of IL-4, IL-17A, INF-α and INF-γ, as well as the increase of pro-inflammatory IL-10 was not significant ($p > 0.05$).

Thus, all patients with DED of various ethiology following the therapy with study drug containing 0.01% dexamethasone phosphate combined with 6% polyvinylpyrolidone and 1.5-5.5% dextrose demonstrated the change of local immunity in the form of pro-inflammatory cytokines' levels' decrease and anti-inflammatory cytokines' levels increase.

The dynamics of corresponding parameters of systemic immunity of the same groups of patients is given in Table 5.

Observational stages			Evaluated parameter, pg/ml										
			IL-1β	IL-2	IL-4	IL-6	IL-8	IL-10	IL-17A	IL-1Ra	TNF-α	INF- α	INF- γ
DED due to meibomian blepharitis	Main group (n = 14)	Initial data	36,14 ± 3,27	242,78 ± 13,27	18,60 ± 2,30	16,06 ± 1,44	79,46 ± 4,24	12,86 ± 1,93	200,80 ± 7,16	319,73 ± 17,20	46,80 ± 5,33	30,33 ± 3,63	37,4 ± 6,76
		Day 28 of therapy	24,64 ± 3,06	168,21 ± 42,28	10,53 ± 1,58	6,06 ± 1,29	31,93 ± 2,74	21,13 ± 1,70	154,73 ± 4,40	252,87 ± 8,79	25,40 ± 2,73	10,53 ± 2,36	29,93 ± 5,02
		t	9,3; p < 0,01	6,1; p < 0,05	10,9; p < 0,01	19,6; p < 0,001	35,5; p < 0,001	12,1; p < 0,01	20,6; p < 0,001	13,0; p < 0,01	13,4; p < 0,01	17,2; p < 0,05	3,3; p > 0,05
	Control group (n = 12)	Initial data	35,33 ± 1,97	237,50 ± 6,32	19,33 ± 1,49	16,16 ± 1,35	79,00 ± 2,58	15,33 ± 1,97	205,00 ± 10,50	334,67 ± 16,07	47,50 ± 5,37	26,33 ± 1,49	31,83 ± 6,42
		Day 28 of therapy	28,33 ± 2,11	207,33 ± 6,30	15,16 ± 1,43	11,16 ± 2,03	52,50 ± 3,90	24,16 ± 2,67	161,33 ± 11,05	276,83 ± 17,47	37,33 ± 4,85	15,66 ± 2,36	31,00 ± 3,02
		t	5,0; p < 0,05	7,6; p < 0,01	4,5; p > 0,05	4,6; p < 0,05	12,7; p > 0,05	6,0; p < 0,05	6,4; p < 0,05	5,5; p < 0,05	3,1; p > 0,05	8,6; p < 0,05	0,2; p > 0,05
DED due to perimeno-pause	Main group (n = 16)	Initial data	30,44 ± 3,92	244,81 ± 8,35	23,69 ± 1,61	20,19 ± 3,07	82,87 ± 4,06	13,56 ± 3,84	212,94 ± 22,56	326,06 ± 7,89	41,62 ± 3,69	18,43 ± 2,98	31,44 ± 11,20
		Day 28 of therapy	16,94 ± 1,64	187,12 ± 5,90	9,56 ± 1,58	10,25 ± 2,47	32,44 ± 2,74	28,81 ± 2,32	165,12 ± 5,95	258,68 ± 4,64	21,69 ± 2,66	6,74 ± 1,34	21,93 ± 5,14
		t	12,4; p < 0,01	21,9; p < 0,001	24,4; p > 0,05	9,6; p < 0,01	40,0; p < 0,001	13,3; p < 0,01	7,9; p < 0,05	28,8; p < 0,05	17,0; p < 0,001	12,94 p < 0,01	5,3; p > 0,05
	Control group (n = 18)	Initial data	36,11 ± 1,52	241,55 ± 7,97	29,11 ± 4,17	19,44 ± 2,26	91,11 ± 9,75	14,66 ± 1,74	204,11 ± 6,05	330,11 ± 7,15	43,77 ± 3,11	29,66 ± 5,49	35,44 ± 9,86
		Day 28 of therapy	29,66 ± 4,39	206,55 ± 8,19	17,22 ± 3,64	11,77 ± 1,81	54,44 ± 10,99	21,22 ± 3,94	182,88 ± 9,54	283,33 ± 12,87	30,88 ± 2,76	20,33 ± 1,15	22,55 ± 4,83
		t	3,9; p > 0,05	8,7; p < 0,01	6,1; p < 0,05	7,5; p < 0,05	7,1; p < 0,05	4,3; p > 0,05	5,3; p > 0,05	9,0; p < 0,05	8,8; p > 0,05	4,7; p > 0,05	3,2; p > 0,05
DED due to Sjögren's syndrome	Main group (n = 20)	Initial data	36,75 ± 3,25	309,55 ± 8,66	29,80 ± 3,04	26,15 ± 2,63	75,65 ± 15,35	9,55 ± 1,96	224,75 ± 6.03	330,65 ± 8,30	48,05 ± 2,48	21,30 ± 2,93	42,30 ± 8,70
		Day 28 of therapy	15,40 ± 2,33	183,15 ± 11,4	13,80 ± 2,36	14,05 ± 1,56	25,05 ± 4,05	21,75 ± 2,55	168,45 ± 4,74	266,35 ± 7,80	27,30 ± 2,59	11,35 ± 1,56	22,70 ± 6,74
		t	23,5; p < 0,01	38,5; p < 0,05	18,2; p > 0,05	17,3; p < 0,01	13,9; p < 0,01	17,9; p < 0,05	32,2; p < 0.001	24,6; p < 0,05	25,3; p < 0, 05	13,1; p < 0, 01	7,8; p > 0,05
	Control group (n = 20)	Initial data	35,80 ± 3,54	311,10 ± 13,26	28,80 ± 2,85	24,80 ± 1,72	75,60 ± 4,10	8,60 ± 1,57	227,40 ± 6.51	341,630 ± 10,67	49,00 ± 2,53	19,33 ± 2,36	40,80 ± 11,85
		Day 28 of therapy	28,10 ± 2,25	252,80 ± 11,49	24,00 ± 1,95	15,70 ± 2,00	40,50 ± 5,54	16,30 ± 1,67	163,40 ± 10,99	290,10 ± 13,11	36,40 ± 3,77	10,60 ± 1,354	30,50 ± 8,17
		t	5,5; p > 0,05	10,0; p < 0,05	4,2; p > 0,05	10,3; p < 0,05	15,3; p < 0,05	10,1; p < 0,05	15,1; p > 0,05	9,1; p < 0,05	8,3; p > 0,05	9,7; p < 0, 05	2,2; p > 0,05

Table 5: Some immunity parameters in the blood plasma of patients with DED of various ethiology following the therapy performed.

As seen from the data in the Table 5, after the therapy with study drug a change of controlled parameters in peripheral blood was observed. In particular, in patients with DED due to meibomian blepharitis following the therapy performed blood plasma showed the decrease against initial levels of IL-1β 1.5 times ($p < 0.01$), IL-2 - 1.4 times ($p < 0.05$), IL-4 - 2.7 times ($p < 0.01$), IL-6 - 2.5 times ($p < 0.01$), IL-8 - 2.5 times ($p < 0.001$), IL-17A - 2.5 times ($p < 0.001$), IL-8 - 2.5 times ($p < 0.001$), IL-17A - 1.3 times ($p < 0.01$), IL-1Ra - 1.2 times ($p < 0.01$), TNF-α - 1.8 times ($p < 0.01$). At that, the level of anti-inflammatory cytokine IL-10 increased 1.6 times ($p < 0.01$).

In the control group, on day 28 of therapy the blood plasma showed the decrease against the initial levels of IL-1β 1.1 times ($p < 0.05$), IL-2 - 1.1 times ($p < 0.05$), IL-6 - 1.4 times ($p < 0.05$), IL-17Ав - 1.2 times ($p < 0.05$), IL-1Ra - 1.0 times ($p < 0.05$), INF-α - 1.3 times ($p < 0.05$). It should be mentioned, that the level of anti-inflammatory cytokine IL-10 increased 1.2 times ($p < 0.01$). However, the decrease of IL-4, IL-8, TNF-α and INF-γ was not statistically significant compared to their levels in blood plasma prior to therapy ($p > 0.05$).

The results of pro- and anti-inflammatory cytokines in blood plasma in patients with DED due to perimenopause showed the decrease of IL-1β 1.7 times ($p < 0.01$), IL-2 - 1.3 times ($p < 0.001$), IL-6 - 2.0 times ($p < 0.01$), IL-8 - 2.6 times ($p < 0.001$), IL-17A - 1.3 times ($p < 0.05$), IL-1Ra - 1.3 times ($p < 0.05$), TNF-α - 1.9 times ($p < 0.01$), INF-α - 2.6 times ($p < 0.01$). However, the decrease of IL-4 and INF-γ was not statistically significant ($p > 0.05$). At that, the level of IL-10 increased 2.1 times ($p < 0.01$).

In the control group, following the therapy performed the blood plasma tests showed the decrease against initial levels of IL-2 - 1.2 times ($p < 0.01$), IL-4 - 1.2 times ($p < 0.05$), IL-6 - 1.4 times ($p < 0.05$), IL-8 - 1.2 times ($p < 0.05$), IL-1Ra - 1.2 times ($p < 0.05$). However, the decrease of IL-1β, IL-17A, TNF-α,INF-α and INF-γ, as well as the increase of pro-inflammatory cytokine IL-10 did not show statistically significant changes against the initial levels prior to tear replacement therapy ($p > 0.05$).

The results of blood plasma tests in patients with DED due to Sjögren's syndrome following the therapy performed showed the decrease of IL-1β 2.4 times ($p < 0.01$), IL-2 - 1.7 times ($p < 0.05$), IL-6 - 1.8 times ($p < 0.01$), IL-8 - 3 times ($p < 0.01$), IL-17A - 1.3 times ($p < 0.001$), IL-1Ra - 1.2 times ($p < 0.05$), TNF-α - 1.7 times ($p < 0.05$), INF-α - 1.9 times ($p < 0.01$). As in previous groups, the decrease of IL-4 and INF-γ levels was not statistically significant ($p > 0.05$). At the same time, the level of IL-10 on the background of therapy increased 2.3 times ($p < 0.05$).

In the control group of patients with DED due to Sjögren's syndrome blood plasma tests showed the decrease of IL-2 1.2 times ($p < 0.05$), IL-6 - 1.1 times ($p < 0.05$), IL-8 - 1.5 times ($p < 0.05$), IL-1Ra - 1.1 times ($p < 0.05$), INF-α - 1.3 times ($p < 0.05$). However, the decrease of IL-1β, IL-4, IL-17A, TNF-α, INF-γ and the increase of IL-10 were not significant ($p > 0.05$).

Thus, all main groups of patients with DED of various ethiology demonstrated following the therapy performed the change of total immunity in the form of the decrease of pro-inflammatory cytokines' level and increase of anti-inflammatory ones.

Comparative analysis of the blood plasma and tear fluid cytokines' levels in DED of various ethiology showed a common trend: levels of TNF-α, IL-6, IL-2 in tear fluid are more than 2 times higher than their levels in blood plasma, thus confirming the important role of local cytokines' production in the development of chronic inflammation of the ocular surface tissues.

Conclusion

The results of the comprehensive clinical and functional study, as well as laboratory research prove the high clinical efficiency of the developed medication that has a marked local anti-inflammatory effect in the therapy of corneal-conjunctival xerosis of various ethiology.

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