



ISSN: 2395-6429

THE EYE DROPS' OSMOTIC CONCENTRATION AND THEIR UTILIZATION IN KERATOCONJUNCTIVIS SICCA TREATMENT

¹František Dorko, ²Pavel Giacintov, ²Renata Giacintová, ²Aneta Giacintov, ²Pavel Rezek and ¹Alžběta Grussmannová

¹Department of Anatomy, University of Ostrava, Faculty of Medicine,
Syllabova 19, Ostrava, Czech Republic
²Eye Clinic, Česká 1, Brno, Czech Republic

ARTICLE INFO

Article History:

Received 27th February, 2017
Received in revised form 11th
March, 2017
Accepted 7th April, 2017
Published online 28th May, 2017

Key words:

eye drops' osmotic concentration, tear film, sicca syndrome, keratoconjunctivis sicca, TearLab, dry eyes syndrome

ABSTRACT

Sicca syndrome, or more precisely keratoconjunctivis sicca, is a multifactorial disease which is bound to the conditions of neighbouring environment, and also tends to be associated with variety of both local and systemic illnesses. Dry eyes syndrome leads either to unpleasant subjective difficulties, or worse, to the affection of the visual acuity or the outer part of an eyeball. Nowadays, dry eyes syndrome is considered to be a lifestyle disease. According to a number of sources, up to 20% of patients show signs of this disease. Prevalence grows increasingly after fifty years of age; women tend to be inclining to this disease twice more than men.

By the essential illness's early diagnosis and treatment complemented with appropriate preparations, we can contribute to improvement of quality of patient's life and prevent creating serious complications which are violating the visual acuity. It is the TearLab machine, which measures the osmotic concentration of patient's tears in an outpatient and non-invasive way, that is instrumental in a quicker diagnosis and choice of a correct preparation. Based on measured value of patient's tears, the doctor appoints the suitable and convenient choice of preparation according to the osmotic concentration.

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INTRODUCTION

Preface

The keratoconjunctivis sicca diagnosis negatively influences the adhesions of tear film and both cornea and conjunctiva; the consequence of this phenomenon is a dry eye feeling and also pathological changes on cornea and conjunctiva. The prominent sign of various dry eye syndrome manifestations is an abnormal composition of tear film, containing an insufficient quality and quantity of tears. According to the causes of creation we can distinguish two types of dry eyes syndrome: aqueous tear-deficient keratoconjunctivis sicca and evaporative keratoconjunctivis sicca.

The aqueous tear-deficient keratoconjunctivis sicca shows an insufficient quantity of tears' hydrophilic component and commonly occurs after cornea refractive interventions. The evaporative keratoconjunctivis sicca is characteristic by an excessive tears evaporation, which is caused by malfunctioning of the lipophilic layer of the cornea. Risk factors for dry eye syndrome development include staying in dry air-conditioned environment, hormonal changes in organism (pregnancy, menopause), kidney disorders, age,

usage of some medicaments (antidepressants, antihistamines, diuretics, antiglaumatics, hormonal therapy, antidiabetics, medicaments used for autoimmune diseases or those for thyroid gland malfunctions), and also both genetic and environmental factors.

Sicca syndrome

The notional circulus vitiosus of dry eyes syndrome lies in tear film instability, as it loses hydration due to evaporation of water component, which leads to osmotic concentration increase. Because of its stressogenic potential, hyperosmolarity causes a surface inflammation, accompanied by increasing instability of tear film. Subjectively, the dry eye syndrome is perceived as an itching or burning feeling in the eye, foreign body sensation, or frequentative lachrymation. Objectively, the dry eye syndrome can be diagnosed thanks to a variety of specific tests. On the slit lamp, the height of tear meniscus, lid margin, Lid Parallel Conjunctival Folds (LIPCOF), and Meibomian glands is rated, cornea dying by fluorescein is done, or the time of tear film recovery after blinking is measured (Tear Break-up Test, TBUT). The most common objective test, which rates the tears' quantity, is Schirmer test. The degree of lachrymation is measured by a strip of filter

paper, which is placed behind the eyelid on the surface of the conjunctiva. The clinical method for tear film rating according to its quality is a test to determine the presence of inflammatory markers (e.g. Matrix metalloproteinase 9, MMP-9) or osmotic concentration of tears measuring.

Osmotic concentration indicates the amount of osmotically active substances in one liter of solution. Osmotically active substances do not permeate the membrane, regardless on their size or electric charge. The unit of osmotic concentration is mOsm/l. Osmolarity is the number of miliosmoles/ liter (mOsm/ l) of solution. The tear and cornea osmotic principle is identical with the physiological osmotic activity of cells in other organism's tissues.

Tab 1 Osmolarity values of eye preparations.

Brand Name	Osmolality mOsm/kg	Density kg/l	Osmolarity mOsm/l
Otc Eye Treatments			
Eye drops			
Allergo-comod	317	1,0260	309
Cationorm	195	0,9975	195
Hyabak protector	208	1,0006	208
Hyal drop	287	1,0060	285
Hylo-comod	293	1,0190	288
Hylo-fresh	273	0,9968	274
Hylo-parin	301	1,0129	297
Hylo-protect	282	1,0034	281
Optive	353	0,9570	369
Optive fusion	331	1,0052	329
Systane balance	276	1,0220	270
Systane hydration	275	0,9976	276
Systane ultra	300	1,0020	299
Tears naturale II	296	0,9660	306
Thealoz	324	1,0140	320
Thealoz duo	201	1,0106	199
Unitears	289	0,957	302
Visine classic	288	1,0204	282
Eye gels			
Hylo-gel	289	1,0234	282
Recugel	325	1,6637	195
Systane gel drops	294	0,9108	323
Vidisc gel	243	1,0852	224
Rx Eye Treatments			
Flarex	300	0,987	304
Ophthalmol-Septonex	315	0,9980	316
UNITROPIC	301	1,0039	300
Topical antihistamines			
Emadine	292	0,9750	299
Livostin	1023	1,0041	1019
Spersallerg	296	0,9790	302
Zaditen SDU 0,025 amp. 30x0,4ml	241	0,9952	242
Topical antibiotics			
Floxacil	356	1,0116	352
Maxitrol	284	1,0183	279
Tobradex	303	1,0202	297
Antiglaucomatics			
Alphagan	328	0,9930	330
Arulatan	266	0,9740	273
Azarga	294	1,0320	285
Azopt	302	1,0200	296
Cosopt	272	0,9350	291
Cosopt free	272	0,8948	304
Duotrav	296	0,99	299
Ganfort	284	1,0077	282
Lumigan	292	1,0020	291
Luxfen	302	0,9810	308
Travatan	280	0,996	281
Trusopt	289	0,9714	298
Xalatan	264	0,998	265
Topical NSAIDs			
Arufil	311	1,0160	306
Nevanac	285	1,1009	259
Yellox	303	1,0171	298
Eye Lotions			
Eye WATER magistraliter	271	0,997	272

In the hypertonic environment, the cell loses its water component and gets dehydrated. In the hypotonic environment, the edema is created due to hydrophilic behaviour of the cell. If the cell is located in the isotonic environment, there is no exchange between water molecules.

Physiological values of tears' osmotic concentration range between 295 – 310 mOsm/l. With the increasing age, the value of osmotic concentration slightly increases physiologically, too. Dry eyes syndrome is characteristic by tears' osmotic concentration above 315 mOsm/L.

Due to its mechanism, the increased osmotic concentration causes inflammatory reaction, leading to violation of surface parts of an eye. Hyperosmolarity activates inflammatory cells' cascades on the epithelium of the cornea, which inflicts inflammation mediators' release, and further apoptosis of cornea's external epithelioidal cells and conjunctiva's cells. Production decrease or increased tears evaporation increases the value of osmotic concentration. This condition is the cause of the apoptosis of cells which are located in epithelial and conjunctival section; simultaneous production of thicker tears causes Meibomian glandes blocking, and their consecutive atrophy.

MATERIAL AND METHODS

When using an outpatient method, osmotic concentration was measured by the TearLab machine. This method is simple, quick and not unpleasant for the patient. We removed a small sample of tears from the surface of an eye with a disposable polycarbonate microchip (by passive capillary action, there is 50 nl, 5×10^{-9} l of tears taken into the microfluidic duct in the microchip); we also analysed and evaluated the sample immediately. For an indirect assessment of osmotic concentration, TearLab uses thermally rectified measuring of tears' impedance.

Pic. 1: Sampling of the tear film.

We analysed the selected samples of eye drops with an osmometer Fiske One; the sample of 15 microliters volume, ranging from 0 to 2000 mOsm/kg, with +/- 2 mOsm/kg precision.

Osmolality indicated the quantity of all osmotically active substances within a kilogram of the measured substance. The unit is mOsm/kg. To get a precise conversion of osmolality and osmotic concentration, we measured the density of drops and converted osmotic concentration from osmolality. Tested samples came from the distribution for Czech and German markets.

The osmotic concentration values for the Czech market, containing also lubricants and ophthalmologicals, are stated in the chart.

RESULTS

Measuring of tears' osmotic concentration took place in MUDr. Pavel Giacintov's eye surgery in Brno. The measuring was done by TearLab machine. Before the measuring itself, the patients were given detailed information about the purpose of the internal clinical research and they also submitted a written agreement which concluded that they were thoroughly informed and they agreed with providing personal data. Twenty-five patients (n=25), aging from 11 to 81 years,

diagnosis, as it has the highest ratio of sensitivity and specificity of the test (72,8%, respectively 92%) in comparison with the other tests. For comparison, we can mention Schirmer test which has high specificity but low sensitivity (79, 5%, respectively 50,7%).

We also investigated the influence of contact lenses on tear film's osmotic concentration as a part of our test. The osmotic concentration increase based on dependence on a contact lens on the cornea has been detected. The research divided examined subjects into four groups, according to the type of contact lenses (diurnal, highly hydrophilic, with a lower content of a hydrophilic component, and RGP lenses). The initial value of osmotic concentration was identical within all four groups. With the contact lens application, the osmotic concentration value statistically significantly increased to 315 mOsm/l. However, the differences between various types of contact lenses themselves are not so statistically significant. The presence of the contact lens on a cornea leads to tear film osmotic concentration increase. As a result, an applied contact lens leads to tear film's physiological stability violation, evaporation increases, cornea vulnerability decreases, and the final consequence is depreciatory tear secretion, followed by osmotic concentration increase.

It was the subject of the research whether the value of eye drops' osmotic concentration value influences the effectivity of dry eyes syndrome therapy. The research included 28 patients, to whom two types of eye drops with 0, 4% hyaluronic acid in a water solution were applied. The first type of eye drops belongs to hypoosmolar category (150 mOsm/l), and the second one was isoosmolar (300 mOsm/l). According to both patients' subjective evaluation and more satisfying objective results, hypoosmolar eye drops came out of the test as the better ones.

Thanks to hypoosmolar drops applied on a hyperosmolar tear film, the concentration of ions (leading to osmo-correction) in patients' tears is balanced. Theoretically, also the application of hyperosmolar eye drops on the hyperosmolar tear film within the sicca syndrome can have a positive effect. Epithelial cells tend to swell in dependence on cells' membranes corruption. By adding hyperosmolar solution on such a surface of a cell, the volume is reduced and the physiological state is established.

Purposeful substantial hyperosmolar dehydration can be practically utilized with, for example, cornea edema. Causally, for the edematous cornea treatment is most commonly used the 5% sodium chloride substance; thanks to this substance, the tear film osmotic concentration on the cornea increases. To gain the osmotic concentration balance, molecules of water has to be transferred to disadvantage cells on the cornea surface; pachymetry therefore decreases and the edema is minimized.

Dry eyes syndrome symptoms increase significantly with age. Based on discovered information, the dry eyes syndrome prevalence within the studied sample of population is higher among women, especially in an elder age. The knowledge of tears' osmotic concentration helps with choosing the most efficient dry eye syndrome therapy. It is possible to choose on purpose the most appropriate eye drops, material of applied eye lenses, respectively make a combination of a therapy and lachrymal implants application.

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