Drug Report
Hyaluronic acid

Treatment of Sicca Syndrome –
Effective and well-tolerated also with contact lenses

Translation

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Editorial

The incidence of the Sicca Syndrome has increased significantly over the past 10 years. In the meantime it is at the top of the most frequent ocular diseases world-wide. The treatment with preparations to lubricate the surface of the eye is therapy of choice at present. Apart from an increased viscosity of eye drops, further product characteristics are important to be able to treat patients with moderate or severe symptoms successfully. A good adhesion to biological membranes, ensuring full visual function and wound healing capabilities are examples for these characteristics.

Hyaluronic acid is ideally suited as an ingredient for lubricating eye drops due to its good water binding properties, the elastic flow characteristics and the good tolerance profile. Not least because of the excellent tolerance has hyaluronic acid proven to be successful with Sicca patients wearing contact lenses. In the past however, two factors repeatedly caused problems. First, preservatives contained in the solution can damage the tear film as well as the contact lenses. Second, phosphate-based buffer systems contained in eye drops can cause the formation of water-insoluble calcium phosphate in the outer cell layers of the cornea. Both problems can be fought effectively by now: The use of special application systems supersedes preservatives and citrate buffer systems can replace phosphate buffers as they achieved the same level of efficacy and improved tolerance.

This overview report will present hyaluronic acid as standard substance for the treatment of Sicca Syndrome. It will also reveal important criteria for the choice of lubricating eye drops with regard to the special circumstances concerning the eye of the contact lens wearers as well as the different contact lens materials.

Prof. Dr. med. Christian Teping

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Hyaluronic acid

Treatment of Sicca Syndrome - effective and compatible also with contact lenses

The treatment of Sicca Syndrome sets high standards to lubricating eye drops. Hyaluronic acid binds moisture and demonstrates a wetting behaviour which is adapted to the physiology of the eye. Together with special flow properties of solutions containing hyaluronic acid, an intensive and constant eye lubrication can be achieved. The tolerance of eye moisturizers is especially important to wearers of contact lenses and in case of frequent application. Tolerance problems can be prevented effectively by the use of preservative-free application systems and the replacement of phosphate buffers by buffer systems containing citrate.

The Sicca Syndrome, also known as keratoconjunctivitis sicca or “dry eye”, is a disease with increasing importance for the ophthalmologic practice. Its prevalence estimation is difficult due to the heterogeneity of the symptoms. A recently published paper has taken into account the definition criteria valid since 2007 (overview 1) and indicates for example that the Spanish population shows a prevalence of 11.9% among adult females and 9% among adult males [30]. The gender-specific differences observed here are even more clear-cut in another examination of Japanese employees (21% of the females and 10.1% of the males) [28].

Overview 1:
Valid definition of the Sicca Syndrome since 2007 according to the “Definition and Classification Subcommittee of the International Dry Eye Workshop (DEWS)” (Lemp et al. 2007)

“The Sicca Syndrome is a multifactorial disease of the tear film and the surface of the eye which manifests in form of discomfort, visual impairment and instability of the tear film causing potential damage of the surface of the eye. It is associated with an increased osmolarity of the tear film and inflammatory processes at the cornea and conjunctiva.”

The Sicca Syndrome may have far-reaching consequences on the quality of life of affected patients thereby causing considerable economic damage. The exact determination of the therapy costs is difficult - as preparations for the treatment of Sicca Syndrome can only be prescribed in Germany in exceptional cases - however the size of the market of tear substitutes alone added up to 54 Mio. Euros in Germany in 2008.
The objective of the therapy is an intensive and constant lubrication

Treatment of Sicca Syndrome - effective and compatible also with contact lenses

Overview 2:
The most important requirements for lubricating eye drops:

- Binding of moisture (water transport)
- Dispersion of lachrymal fluid (wetting)
- Duration of lubrication

The basis of a therapy of the Sicca Syndrome is the supplementation of missing or unphysiologically composed lachrymal fluid by means of lubricating eye drops. Due to the complexity of the disease, the difficult structure of the tear film and the special anatomic and physiological properties of the surface of the eye, different standards have to be set for substances to compensate a deficiency of tears (overview 2). Apart from the capability to bind moisture, wetting properties are particularly important as the surface of the cornea and conjunctiva are rather hydrophobic. Constant wetting of the surface of the eye can be achieved physiologically by secretion of certain glycoproteins which form the so-called mucin layer. Substances for the compensation of tear deficiency have to take into account the physiological properties and need to have lubricating properties as well.

While the potential for water transport and wetting of ocular surfaces is of particular importance to the intensity of the moistening, the duration of the moistening depends on an additional parameter: the viscosity of the solution. An increase in viscosity of aqueous solutions is generally achieved by means of expandable substances with gel-forming properties. Thus, the currently available tear substitutes contain almost without exception film-forming substances based on polymers. However, the increase in viscosity of solutions for the moistening of the eye is only possible and useful to a certain extent as an impairment of vision sets in above substance-specific limits.
Hyaluronic acid had been isolated for the very first time in 1934 by Meyer and Palmer [17]. At that time, vitreous bodies of cow eyes were used as a biological resource for this compound. They soon realized that hyaluronic acid is much more common in the organism of vertebrates than anticipated. Among others, hyaluronic acid is part of the extra cellular matrix of the conjunctival tissue, the cartilage as well as the synovial fluid. Beyond that, hyaluronic acid had been detected in the cell membrane of a variety of different bacteria [2]. Over the course of time, this fact provided the opportunity for today’s obligatory biotechnological production of hyaluronic acid.

Especially in ophthalmology, the clinical benefit of the use of aqueous solutions of hyaluronic acid had been identified early. Hyaluronic acid preparations ensure a reliable protection of the corneal endothel during eye surgery. Furthermore, hyaluronic acid solutions help maintaining size and form of the anterior chamber in cataract surgery and thereby reduce the risk of prolapse [10]. Contrary to the air used in this procedure, the surgeon is able to recognize intraocular structures clearly [1]. During keratoplasty, hyaluronic acid solutions are used as buffer for the donated cornea. With this, the endothelial cell loss can be decreased in comparison to BSS (balanced saline solution) which is normally used in this procedure. Additionally, hyaluronic acid displays healing effects in the contact zone between the body’s own tissue and the donor cornea.

Sicca patients profit especially from the characteristics of hyaluronic acid. This can be proven by its molecular structure and the physical-chemical properties of its aqueous solutions.

Hyaluronic acid is a polymer made of linearly arranged and alternatingly connected units of D-glucuronic acid and N-acetyl-glucosamine (image 1).

Image 1: (please refer to original document) Structural formula of hyaluronic acid

The degree of polymerization and the resulting molecular weight of hyaluronic acid shows a big variety depending on the origin and the purification process. The chain length of hyaluronic acid molecules is of high relevance for the clinical use of this substance as this parameter determines significantly the viscosity and the flow behaviour of its aqueous solution. With increasing degree of polymerization a stronger convolution of molecule chains (entanglement formation) can be observed causing a special rheology of the aqueous hyaluronic acid solutions. The interaction between chains of hyaluronic acid occurring during entanglement formation lead to a non-Newtonian flow behaviour which is characterized by a comparatively high viscosity while little shear stress is executed to the solution. However, the viscosity may decrease if the solution is subjected to greater shear stress during mechanical load. Once the mechanical influence has terminated, it returns to the baseline value in a short time [10, 16]. If we relate this to the conditions in the eye, it means that during a blink of the eye lid a transient decrease of the solution’s viscosity results facilitating an even distribution of the solution on the surface of the eye without visual disturbances.
Viscosity determines the efficacy and the duration of lubrication

The viscosity of a hyaluronic acid solution is essential for an effective and constant lubrication of the surface of the eye. However, a high hyaluronic acid concentration as sole criterion for the evaluation of viscosity is not sufficient to assess the properties of a formulation as the viscosity is not only determined by the solution’s concentration but the molecular weight of the applied hyaluronic acid as well. Thus, the use of high-molecular and thereby long-chained hyaluronic acid leads to a higher viscosity of the solutions compared to similar concentrations of hyaluronic acid with lower molecular weight. It means that viscosities of similarly concentrated solutions can differ significantly and, by implication, its duration and effectiveness of moistening, too. The comparability of eye moisturizers with different hyaluronic acid qualities and different hyaluronic acid content is facilitated by calculating the product of the percentage of concentration, molecular weight and viscosity (chart 1, image 2). With regard to good tolerance and effectiveness particularly those eye moisturizers can be recommended that achieve high viscosity values with low or average hyaluronic acid concentrations. A maximum limit has to be taken into account as an impairment of vision may result if the grade of polymerization and thereby the molecular weight of the applied hyaluronic acid exceeds certain limits. Studies have revealed that this impairment emerges at a concentration of 0.25% hyaluronic acid beyond a molecular mass of 4x10^6 Dalton [15].
Additional effects of hyaluronic acid

Apart from simple moistening, hyaluronic acid has additional effects on the corneal surface. In-vitro studies on the human cornea epithelial cell culture model have shown that hyaluronic acid solutions can increase the migration of epithelial cells significantly. This discovery is based on the fact that molecules of hyaluronic acid serve as ligand for CD44-adhesion molecules on the cellular surface [11]. Increased cell migration can boost the healing process of superficial cornea lesions.

**Image 2: (please refer to original document)** Comparison of different eye moisturizers based on the product of hyaluronic acid concentration, molecular weight and viscosity.

Hyaluronic acid concentration (%) x molecular weight (Da) x viscosity (mm²/s) x 10⁶

**Chart 1:** hyaluronic acid concentration, molecular weight and viscosity of different eye moisturizers.

<table>
<thead>
<tr>
<th>Investigated Product</th>
<th>Hyaluronic acid (a)</th>
<th>Molecular weight (Da)</th>
<th>Viscosity (mm²/s) (c)</th>
<th>Product (a)(b)(c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GenTeal™ HA (Novartis)</td>
<td>0.1%</td>
<td>1.9×10⁶</td>
<td>5.4</td>
<td>1.03×10⁶</td>
</tr>
<tr>
<td>HYABAK® (Thea Pharma)</td>
<td>0.15%</td>
<td>0.4×10⁶</td>
<td>2.6</td>
<td>0.16×10⁶</td>
</tr>
<tr>
<td>HYLO®-GEL (URSAPHARM)</td>
<td>0.2%</td>
<td>2.1×10⁶</td>
<td>50</td>
<td>21×10⁶</td>
</tr>
<tr>
<td>HYA-OPHTAL® System (Winzer)</td>
<td>0.24%</td>
<td>0.75×10⁶</td>
<td>11</td>
<td>1.98×10⁶</td>
</tr>
<tr>
<td>HYLO-VISION® GEL MULTI (Omnivision)</td>
<td>0.3%</td>
<td>0.8×10⁶</td>
<td>44</td>
<td>10.56×10⁶</td>
</tr>
</tbody>
</table>

Additionally, hyaluronic acid shows proliferation promoting properties [13]. While the effect of the hyaluronic acid as physical visco-elastic protection barrier of the cornea and conjunctiva correlates with the degree of polymerization, the wound-healing properties are obviously rather a function of the solution's concentration.

**In-vivo** examinations about wound healing of artificially caused damages of rabbit cornea show an improvement in wound healing which is measurable at a concentration of 0.1% in comparison to the control group and shows a statistic significance at 0.2% [4]. In another examination, the effect of the hyaluronic acid solution already reached the significance level at a concentration of 0.1% [3].

Moreover, a recent in-vitro and in-vivo study revealed a protective effect during the use of hyaluronic acid solutions with high molecular weight and a concentration of 0.2% [24].
Apart from high effectiveness by intensive and constant lubrication, compatibility with contact lenses is another important quality feature of moisturizers. Due to the fact that contact lenses are foreign bodies which interact with the physiological processes of tear production, contact lens wearers in particular require a preparation for the care of the eye surface that will not turn into an additional burden on the eye. Contact lens wearers are inclined to develop Sicca Syndrome per se due to reflectorical hyposecretion of lachrymal fluid. They also show a high risk for the progression of the disease up to the point where lesions of the corneal epithelium can occur as a consequence of mechanical stress. Another implication of the interaction between contact lens and eye is an increased osmolarity of the lachrymal fluid which promotes the emergence of the Sicca Syndrome [7, 9, 19]. The separation of the lachrymal fluid into a tear film in front of the contact lens and behind accelerates the evaporation of humidity from the surface of the eye. All these factors lead to the conclusion that 50% of contact lens wearers complain about symptoms of dry eye syndrome which means that the probability of emergence is 12 times higher in comparison to people with normal vision and 5 times higher compared to wearers of glasses [6, 18, 20].

These numbers clearly show the significance of good tolerance of preparations used for the treatment of dry eye syndrome, particularly for Sicca patients wearing contact lenses. Applied preservatives and buffer systems are the two most crucial factors affecting tolerance.
Preservatives

The quaternary ammonium compounds benzalkonium chloride and cetrimide are still frequently used but due to their physico-chemical properties they are problematic for Sicca patients in general and wearers of contact lenses in particular. With these preservatives, the microbiological safety is opposed to a negative interference with the integrity of the lipid and mucin layer of the tear film (image 3). Furthermore, frequent and intensive contact with the eye surface causes alterations and eventually even damages of the corneal epithelial cells [25, 26]. In the special case of contact lens wearers, the solution containing preservatives diffuses into the space between cornea and lens material and stays there much longer than compared to uncovered eye surfaces due to capillary effects. In addition to this, soft contact lenses in particular have the ability to absorb preservatives due to their hydrogel structure and by this means prolonging the contact time of these substances with the surface of the eye. In-vitro examinations on human corneal cells have shown that one hour of exposure of the surface of the eye to benzalkonium chloride is already sufficient to disrupt the precorneal mucin layer [5]. The frequent application of moisturizers containing quaternary ammonium compounds cause permanent damage of the corneal epithelium. This is especially the case with frequent application which is quite common among patients suffering from pronounced Sicca Syndrome. Additionally, quaternary ammonium chlorides and substances with a similar structure are also known to cause allergies [8, 29]. A more technical aspect is the potential discoloration of soft contact lenses by eye drops containing preservatives.

Image 3: (please refer to original document)
Lipid layer, Aqueous layer, Mucin layer, Corneal epithelium

Oxidative preservatives which recently found their way onto the market of eye drops have the reputation of being more compatible than others. However, this new type of moisturizers has been classified as “slightly eye irritating” by the US American Environmental Protection Agency. As a consequence, the application without reservation is put into perspective particularly in case of frequent use and chronic eye diseases [21].

Sterile application systems - the alternative for preservatives

In order to prevent the negative effects of preservatives on the surface of the eye, sophisticated application systems for a sterile application (e.g. the COMOD® system) are already available [27]. With the aid of a special valve system, the solution contained in the dosing pump does not get in contact with the ambient air. The equalization of pressure after the application of moistening solution takes place by the influx of air through an orifice into a space between the wall of the container and a flexible interior bag which gradually collapses with increasing use of the product. That way, bacteria and other micro organisms cannot get into the interior of the bottle which renders the application of preservatives superfluous. In case of frequent application, products applied by means of such a system have to be preferred to solutions containing preservatives.
Buffer systems

Buffer systems are used in order to keep the pH value of an eye moistening solution in the range of the physiologic pH value of the lachrymal fluid as far as possible (euhydria). The system consisting of sodium-dihydrogen phosphate and its corresponding base sodium-monohydrogen phosphate is widely used in the manufacture of eye drops. Admittedly, reliable pH stabilization can be achieved with it but considerable problems can emerge during the application of buffer systems containing phosphates. In particular frequent application involves the danger that hardly soluble calcium phosphate compounds develop which could lead to precipitations in the cornea. The reaction partner calcium originates from the cytoplasm of corneal cells which have lost their integrity due to mechanical or chemical damage or as a consequence of inflammatory processes. Contact lens wearers are especially vulnerable as contact lenses can cause these superficial lesions. Consequently, permanent calcifications in the cornea may develop which, in extreme cases, can cause persisting impairment of vision among the affected persons.

Citrate buffers as alternative to phosphate buffers

A modern alternative to phosphate buffers is the application of citrate buffered hyaluronic acid solutions. Citrate as opposed to phosphate does not form hardly soluble calcium phosphate compounds as the buffer system consisting of citrate ions also functions as a chelating agent which is able to keep the calcium, contained in the lachrymal fluid, in solution by forming stable complexes. In addition to this, different examinations showed that eye drops containing citrate have wound-healing properties which are based on the inhibition of the infiltration of the inflammed cornea tissue by polymorphonuclear leucocytes [12, 22, 23, 25].
Due to the fact that contact lens wearers are particularly affected by the disadvantages of eye moistening solutions containing phosphate, compatibility with the eye as well as the contact lens material has to be taken into account during the development of moisturizers. For this purpose, a study on the local physiological and material-related tolerance of different contact lens materials was conducted at the Medical Eye-Care Center in Hamburg in 2006 (Dr. med. Gudrun Bischoff). A preservative-free citrate-buffered solution containing 0.1% sodium hyaluronate was used as test substance. During the study 42 Caucasian test subjects at the age of 18 to 65 were treated. Chart 2 displays the type and frequency distribution of the contact lenses used by the test subjects.

**Chart 2: Contact lenses used by the test subjects**

<table>
<thead>
<tr>
<th>Type of contact lens</th>
<th>amount of test subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly contact lenses (hydrogel)</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>Silicon hydrogel lenses</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Conventional lenses (soft)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Rigid gas permeable (RGP) lenses</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>42 (100%)</strong></td>
</tr>
</tbody>
</table>

**Local tolerance**

After a period of 10 days in which citrate-buffered solutions of 0.1 % hyaluronic acid were applied 3 to 6 times a day, not a single test subject showed signs of insufficient tolerance (overview 3). On the contrary, in comparison to the status inquiry at the beginning of the study a slight decrease of the bulbar conjunctival hyperaemia in particular was registered.

**Overview 3:**

No sign of tolerance problems after 10 days

- No sign of increased blood flow or neovascularization of the conjunctiva
- No clinically relevant formation of follicles as expression of inflammatory hypertrophy of lymphatic tissue
- No corneal and conjunctival staining after the fluorescein test

The tear film break up time improves as expected after the application of the moisturizer. Vision also improved slightly at the end of the study period. The objective analysis of anatomic changes at the eye as well as the subjective impressions of the wearers of contact lenses during treatment with moisturizers are both important criteria. Image 4 displays the amount of symptom-free patients applying the citrate-buffered hyaluronic acid solutions utilized in the study divided into different symptom categories.
No symptoms after the application of citrate-buffered hyaluronic acid solution

**Amount of symptom-free patients (%)**
- Burning eyes
- Foreign body sensation
- Itching of the eyes
- Tearing of the eyes
- Pressure sensation
- Formation of mucus

**Material tolerance - wettability of contact lenses**
The properties of the applied lens material mainly determine the grade of moistening of contact lenses. In this case, the water content of the lenses as well as the electric charge of the lens surface play a decisive role. The analysis of the study’s results revealed that the application of citrate buffer systems has no negative influence on the wettability of lens materials and that the solution fully unfolds its moistening properties among contact lens wearers as well.

**Material tolerance - deposition on contact lenses**
As expected, RGP lenses showed no depositions during the study. Soft contact lenses also did not show any sign of depositions that could not be removed. The most frequent changes were detected among wearers of silicon hydrogel lenses which can be explained by the comparatively hydrophobic surface of the lenses associated with the affinity for lipophilic components of the tear film. The more hydrophilic monthly and RGP lenses were less susceptible to depositions. A correlation between the application of citrate-buffered hyaluronic acid solutions and the observed depositions could not be verified.

**Summary of the study’s results**
The study on 42 contact lens wearers with a citrate-buffered hyaluronic acid containing eye moistening solution showed that the replacement of phosphates in eye moisturizers by an alternative buffer system with citrates had no negative repercussions on the wetting properties. The examinations to verify the compatibility of different lens materials also did not show any signs of undesired interaction. There were no irreversible depositions in particular. This can probably be correlated to the good complex forming properties of citrates, thus, keeping potential precipitation forming substances in solution and preventing adhesion on the surface of the lens material.
Conclusion for the clinical use

- Hyaluronic acid solutions facilitate intensive and constant wetting of the surface of the eye
- Concentration and molecular weight of hyaluronic acid solutions are essential for optimal viscosity
- The application of preservative-free hyaluronic acid solutions can prevent the emergence of allergies as well as lesions of the eye
- The application of citrate-buffered systems does not lead to the formation of water-insoluble calcium phosphate and prevents damages of the cornea and permanent depictions on contact lenses
- Preservative-free citrate-buffered hyaluronic acid solutions can be recommended to contact lens wearers in particular as eye moisturizers
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