ARTIFICIAL TEAR SUBSTITUTES: WHICH ONE & WHEN?
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ABSTRACT: Dry eye is a multi-factorial disease; the therapy should improve the symptoms and signs of dry eye as well as address the underlying pathophysiology of the disease. Artificial tear substitutes have been used for treating dry eye syndromes for decades and succeeded in enhancing the comfort of patients. They are currently the main therapy for dry eye and likely to remain the mainstay treatment modality. However, the currently used artificial tears have obvious limitations and its usage has to be personalized based on the patient’s need. This article briefs you on silent features in usage of artificial tears.

KEY WORDS: Dry eye, Tear substitute, Preservatives, Osmolarity

INTRODUCTION: The recent discovery of causes of dry eye and with the advent of better diagnostic testing with more effective therapy has allowed for a better understanding and management of dry eye disease. Dry eye is a multi-factorial disease and is accompanied by increased osmolarity of the tear film and inflammation of ocular surface. The tear film may become damaged under hypertonic stress. Restoring physiologic osmolarity is an important goal in KCS treatment to avoid serious complication. Symptoms of dry eye vary among patients, and most commonly they include itching, grittiness, burning, sensitivity to bright light, foreign-body sensation, irritation, pain, blurred vision, and contact lens intolerance. Dry eyes patients are essentially managed and complications can be prevented by the use of artificial tears and lubricating gels that restore normal tear film. The purpose of tear substitutes used for treatment of dry eyes is to obtain a product that mimics the physical properties of normal tears. The aim of using tear substitutes is to increase humidity at the ocular surface while decreasing evaporation and improving lubrication. Tear substitutes are needed when there is a deficiency of normal tear film. Although the word ‘dry eye’ could literally denote an eye totally devoid of any tear fluid, in its clinical usage it has assumed a far more than the related meaning.

IDEAL TEAR SUBSTITUTE
The solution should be isotonic; i.e., its osmolarity should be approximately 300 mOsm/L. The pH of the solution should be between 6.5 and 7.6. It should be compatible with the natural components of tears and no alteration in the clarity of the aqueous layer should lower the surface tension of the tear film. It should aid in formation of a hydrophilic layer that is compatible with adsorbed mucin, and enhance tear volume. It should significantly reduce the symptoms of dry eye. It should have longer duration of action. Multi-dose products should contain a preservative that poses minimal risk to the corneal epithelium. Products intended for use by patients who require frequent instillation should be preservative-free.

All tear substitutes are formulated as solutions consisting of inorganic electrolytes to achieve tonicity and maintain pH, preservatives to prevent bacterial growth, and water-soluble polymeric systems that can alter the viscosity of the solution and decrease the wetting angle of saline solution on a mucin-free but polymer-coated cornea in vitro. The first step of treatment for dry eyes is to replace the patient's tears with artificial tear drops. It is also well known that tear replacement by topical artificial tears, gels, ointments or lubricants is a widely accepted therapy for dry eyes. Most artificial tear preparations contain cellulose ethers, carbomers, polyvinyl alcohol, polyvinyl pyrrolidone or sodium hyaluronate as their main components.

POLYMERS
CELLULOSE ETHERS, CARBOMERS, POLYVINYL ALCOHOL, POLYVINYL PYRROLIDONES:
Cellulose ethers such as methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and carboxymethylcellulose (CMC) are viscoelastic polysaccharides that increase the viscosity of tears and are sometimes co-formulated with electrolytes as hypotonic solutions and are available as sustained-release tear inserts. Carbomers are viscous synthetic polymers but may be associated with blurred vision. Polyvinyl alcohols are synthetic polymers with low viscosity and adequate water solubility and do not cause visual blur. These colloids dissolve in water to produce solutions of varying viscosities. They have the proper optical clarity and a refractive index similar to cornea, and they are nearly inert chemically. Besides prolonging ocular retention time by enhanced viscosity, these polymers may adsorb at the cornea-aqueous tear layer interface, thereby stabilizing a thicker layer of fluid adjacent to the adsorbing surface. Polyvinyl pyrrolidone (PVP) appears to be capable of forming hydrophilic coatings in the form of adsorbed layers. Polyacrylic acids or carbopol resins, which have greater pseudoplasticity and bioadhesion, are also used to stabilize the tear film. Povidones (polyvinyl pyrrolidones) have good wetting properties when co-formulated with polyvinyl alcohols and are known to be beneficial in mucin layer deficiencies.

SODIUM HYALURONATE: It was recently demonstrated that a hyaluronate receptor, CD44, is expressed in corneal and conjunctival cells and that its activation promotes the interaction with cytoskeletal proteins, suggesting a role for hyaluronate in cell adhesion and motility. Interestingly, it
has been recently reported that the expression of CD44 is increased in patients with moderate dry eye and superficial keratitis and that sodium hyaluronate given for a 2-month period is associated with a decreased expression of this adhesion molecule a recent study carried out on Sjogren’s syndrome patients with severe dry eyes. This study also suggested that a lower osmolarity may be important to obtain a better therapeutic result in patients with highly compromised lachrymal gland secretion, such as Sjogren’s syndrome patients with severe dry eye.

**TABLE 1: Types of tear substitute, chemical properties and its clinical significance**

<table>
<thead>
<tr>
<th></th>
<th>Cellulose ethers</th>
<th>Carbomers (polyacrylic acid)</th>
<th>Polyvinyl alcohol</th>
<th>Sodium hyaluronate</th>
<th>Povidone (polyvinyl pyrrolidone)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Viscoelastic polysaccharides</td>
<td>• Synthetic polymers</td>
<td>• Synthetic polymer</td>
<td>• Mucopolysaccharides</td>
<td>• Synthetic polymer</td>
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<tr>
<td></td>
<td>• Increase the viscosity of tears</td>
<td>• High viscosity when eye is static, shears thin during blinking or eye movement, maximizing thickness of the tear film while minimizing drag</td>
<td>• Low viscosity but optimal wetting characteristics at a concentration of 1.4%</td>
<td>• Viscous formulation</td>
<td>• Co-formulated with electrolytes</td>
</tr>
<tr>
<td></td>
<td>• Sometimes co-formulated with Electrolytes, as hypotonic</td>
<td></td>
<td>• Beneficial in lipid, aqueous, and mucin layer deficiencies</td>
<td>• Viscous formulation</td>
<td>• Superior wetting ability when co-formulated with polyvinyl alcohol</td>
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<td></td>
<td></td>
<td></td>
<td>• Water soluble, does not cause blurring of vision</td>
<td>• Viscosity not influenced by blinking</td>
<td>• Beneficial in mucin layer</td>
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<td></td>
<td></td>
<td></td>
<td>• Short retention time on ocular surface</td>
<td>• CMC forms complex with metabolites or debris in tears</td>
<td>• Deficiency</td>
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<td></td>
<td></td>
<td></td>
<td>• Does not mix well with other ophthalmic products</td>
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OINTMENTS: Patients whose symptoms are not adequately relieved by artificial tear solutions may be treated with more viscous products, such as ointments and tube gels, which make up the second line of therapy for dry eye. Ocular lubricating ointments are bland, non-medicated preparations that are mainly used at bedtime by patients with severe dry eye conditions to provide lubrication of the ocular surface throughout the night. Ointments are typically not suitable for use during the day because of the extent to which they interfere with visual acuity. Thus, nighttime application of an ocular ointment is most commonly used as an adjunct to artificial tear therapy during the day. Because of their increased viscosity, ointments and gels have a longer retention time in the eye. Due to their relatively thick consistency, lanolin- and petroleum jelly-based ophthalmic ointments are especially effective in retarding drainage of the tear film and lubricating the corneal surface.

OTHER VISCOSITY ENHANCING AGENTS: Hydroxypropyl guar is a high molecular weight polymer which mimics mucin layer of tears to prolong contact time and promote retention of 2 viscosity enhancing agents polyethylene glucol and polypropylene glycol. HP –Guar / borate helps to reduce friction coats surface and anionic phospholipids help to stabilize the tear film. After installation of eye drops viscosity decreases as a function of shear rate which is indicative of rapid thinning and mixing. After several blink Ph increases and sorbitol is diluted there is enhanced viscosity from strengthening of the HP – Guar cross-linking.

PRESERVATIVES IN ARTIFICIAL TEAR SUBSTITUTES: One of the most important drawbacks of many of the commercially available artificial tear substitutes and lubricants is the fact that they must contain preservatives, stabilizers, and other additives. These components supply stability and retard germ contamination and growth, thus ensuring the long shelf-life required for commercialization. Even though the concentration of preservatives in artificial tear preparations is generally low, their prolonged presence on an already compromised ocular surface, such as that of a dry eye, can cause serious iatrogenic effects, worsening the ocular surface disease.

The most common preservatives currently used in artificial tear preparations are quaternary ammonium compounds (benzalkonium chloride, benzododecinium bromide, cetrimide, polyquad), alcohols (chlorobutanol), and other compounds (chlorhexidine, sorbic acid, potassium sorbate, boric acid, biguanides, etc). Mercurial agent thimerosal, much used in the past, has been abandoned because of its high potential to provoke not only toxic but also allergic reactions.

Patients who require the application of tear substitutes more than four times daily on a long-term basis to maintain comfort should avoid such preparation and use only unpreserved (usually unit-dose) formulations. Even at low concentrations all the preservatives and buffering agents tested cause some degree of cell damage to ocular tissue as evaluated by corneal and conjunctival cells in tissue culture. With all agents, there was an increased toxicity with increasing concentration. The tested agents in order of decreasing toxicity at the concentrations most commonly used in ophthalmic preparations:

Thimerosal (Thi: 0.01%) > Benzalkonium chloride (BAK: 0.01%) > Chlorobutanol (Cbl: 0.5%) > Methyl paraben (MP: 0.01%) > Sodium perborate (SP: 0.02%) ≈ EDTA.

BAK is the most commonly used preservative in topical ophthalmic medications and is typically used in concentrations varying from 0.015% to 0.05%, although the American College of Toxicology has concluded that BAK can be safely used as an antimicrobial agent at concentrations up to 0.1%. BAK comes from the quaternary ammoniums, which are detergent preservatives and
cationic surfactants. The detergent properties of BAK have been shown to interfere with the integrity of the external lipid layer of the precorneal tear film, reduction of tear film breakup times, and exacerbation of dry eye symptoms. BAK can accumulate in ocular tissue and remain there for extended periods of time, thus prolonging adverse reactions in the cornea. Dose dependency can be seen in BAK because at low concentrations (0.0001%–0.01%), BAK may cause growth arrest or apoptotic mechanisms. However, BAK at higher concentrations (0.05%–0.2%) may cause cell death by necrosis.

Stabilized oxychloro complex (SOC) has been found to have no in vivo or in vitro evidence of cytotoxicity. It is effective at unusually low concentrations (0.005%), which can be degraded into components normally found in tears, such as sodium ions, chloride ions, oxygen, and water. Mammalian cells have oxidases, catalases, and antioxidants that readily neutralize the small amount of SOC generally utilized as a preservative.

Cbl at its most common concentration of 0.5% causes irritation in the eye, which is most likely due to cellular retraction and cessation of normal cytokinesis, cell movement, and mitotic activity. Degeneration of HCEs, generation of conspicuous membranous blebs, cytoplasmic swelling, and occasional breaks in the external cell membrane have also been observed at 0.5%. At a concentration of 0.1%, Cbl caused near depletion of the squamous layer.6

Sodium perborate (SP), like SOC, is readily neutralized by the oxidases, catalases, and antioxidants commonly found in mammalian cells. Unlike SOC however, SP is readily converted into hydrogen peroxide, an efficient antimicrobial, in the presence of water. However, hydrogen peroxide in even small amounts, such as 30 parts per million (0.003%), is known to be somewhat harmful to the eye.5

At clinical concentrations, thimerosal has been shown to directly cause cell death within 9 h, more slowly than BDD and BAK. Within 5 h, thimerosal has been shown to cause severe cell damage in concentrations as low as 0.0005%. It contains an extremely high concentration of mercury (49%).8 Mercury has an extremely high penetration/absorption rate into the ocular tissues greatly potentiating the toxic effects. In fact, thimerosal is so toxic; it is rarely used today in ocular preparations.

DISAPPEARING PRESERVATIVES: These are the preservatives which on contact with eye the preservative is converted to dilute hydrogen peroxide which then changes into water and oxygen within minute of contacting the eye. There are several "disappearing" preservatives used popular in artificial tear products, including Purite (in Refresh products and prescription drugs by Allergan), SOC (Refresh Liquigel), and sodium perborate (in Genteal).

To conclude the use of tear substitute has to be individualized. Use of polyether is mainly for aqueous deficiency and when other adjunctive medications are used as it mixes well with other ophthalmic products. Polyvinyl alcohol is effective in mucin, lipid and aqueous layer deficiencies but it doesn’t mixes well with other products. Povidone iodine is effective for mucin deficiency dry eye. Apart from these the main consideration is the adverse effect of preservatives; hence it is advised to use preservative free tear substitutes for patients who needs frequent installation of medications. Ointments and gel formulations are basically used for night application due to induction of blurred vision if used during waking hours. Apart from the use of artificial tears in the management of dry
eye one has to consider life style changes and other adjunctive treatment like cyclosporine A, tetracycline, punctual plugs etc., has to be kept in mind.

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