Guest Editorial

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Detrimental effects of irrational drug therapy on the ocular surface

The most important guiding principle for most doctors remains do no harm, which in this case is essential to maintain the delicate balance of the ocular surface. With increasing access to healthcare and the ease of application of topical medication they tend to be overused with deleterious effects in the long run. Likewise, topical medications for chronic conditions like glaucoma also contribute to the imbalance in the ocular microbiome. Here we intend to highlight these issues and also discuss their management.

The ocular surface is also exposed to various environmental factors due to the nature of its function and anatomical location. Any disruption in the structure can hamper its functioning and cause damage to the ocular surface. The disorders associated with the ocular surface which includes the cornea, conjunctiva, eyelids and the lacrimal glands are classified as ocular surface disorders (OSD).[1] Clinically, there is a high prevalence of OSD but they remain undiagnosed because of the insufficient understanding of its symptoms and improper evaluation. These disorders include Dry Eye Disease (DED), Allergic eye diseases (AED), blepharitis, meibomian gland dysfunction (MGD), Keratitis, chemical and thermal burns etc. Such diseases can have a severe effect on the eye-sight and in chronic cases, might lead to blindness.

The metabolites of the topical medications generally get deposited in the conjunctival and corneal epithelial basement membrane hence disrupting the surface immune response and result in inflammation of the ocular surface. Most commonly responsible for this are the chronically used medications and preservatives

Glaucoma medication

Glaucoma is the second highest cause of blindness across the world and has been predicted to affect 79.6 million people by year 2020. The initial treatment of glaucoma involves use of topical medications as therapy which results in ocular surface diseases in 50-60% of the patients.[2] Currently used therapies for glaucoma involve the use of prostaglandin analogs, beta-adrenergic antagonists, alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors. The presence of different types of preservatives or even the active part of the medication leads to development or worsening of OSD symptoms.[2] Various studies have shown that as the need for required glaucoma medication increases, there is a rise in the incidence and severity of dry eyes. All the above-mentioned classes of medications have specific adverse effects on the eye and corneal surface. A rise in the incidence and severity of dysfunctional obstructive meibomian gland is observed due to consumption of prostaglandin analogues.[3] The blocking of beta receptors in the lacrimal glands by the use of Beta blockers also leads to a fall in the basal tear turnover rate.[4] Brimonidine tartrate, an alpha- adrenergic agonist shows a rise in the prevalence of ocular allergies in comparison to other prescribed topical medications.[5] In addition to this, due to the use of dorzolamide, a carbonic anhydrase inhibitor, an increase in the corneal thickness has been observed.[6] The patients suffering from any pre-existing OSD experience exacerbation of symptoms such as burning, irritation, itching and fall in visual acuity after consuming topical therapy. In addition to this, patients of primary open angle glaucoma (POAG) that are untreated are partly at an increased risk towards OSD as a 22% fall in basal tear turnover rate is observed when compared to healthy individuals.[7] Also, subconjunctival glaucoma surgeries have an increased failure rate in patients with ocular surface disorders.

Other than the prolonged use of topical medication for management of glaucoma, increased intraocular pressure and inadequate functioning of the endothelial pump mechanism also contribute to the disruption in the ocular surface microenvironment.

Preservatives

For prevention of microbial contamination, preservatives are commonly used in lowest possible concentrations in medications. Currently, preservatives added in medications for glaucoma comprise of Benzalkonium chloride (BAK), stabilized oxychloro complex added in Alphagan P, sofZia preservatives added in Travatan Z and formulations of Polyquaternium-1 used in

Travatan formulations.[8,9] Usually these added preservatives target the cell walls of bacteria and also improve the penetration of drugs within cornea. The most commonly used preservative is BAK, which leads to the initiation and worsening of OSD by the destabilization of goblet cells and the tear film. BAK preservatives affect the conjunctival epithelium by inducing squamous metaplasia that leads to the disruption of corneal epithelium due to loss of epithelial cell density and an increase in activation of stromal keratocytes.[10] Various animal studies have concluded that ocular surface effects of BAK are concentration dependent such that its higher concentrations lead to more corneal damage as well as infiltration of the conjunctiva.[11] Even though BAK shows higher level of ocular surface toxicity, it shows the highest effectiveness for the inhibition of microbial growth in medicines when compared to the newer preservatives.[12]

Topical anesthetic abuse

In ophthalmology, topical anesthetic drugs find a wide range of application for diagnosis and surgeries. These anesthetics include proparacaine, tetracaine, lidocaine and benoxinate cocaine that function by blocking of sodium channels within the neuronal axons which keeps the brain from detection of pain stimuli.[13] These drugs are usually well-tolerated but can cause severe toxic effects when abused. The ocular surface is commonly affected due to the abuse of such anesthetics as they can cause permanent damage to the corneal surface by deep infiltration of cornea, corneal ulceration and loss of visual acuity.[14] Punctuate corneal epithelial erosions are observed during routine administration of topical anesthetics along with evidence of epithelial toxicity. It can be seen in the form of corneal drying due to the loss of corneal sensations leading to a fall in blinking rate and tear production.[15] Migration of corneal epithelial cells is inhibited due to such anesthetics which leads to impaired healing and chronic defects within the eye. In addition to this, anesthetic toxicity can show symptoms that mimic other conditions like neurotrophic ulcers and refractory corneal lesions. There have been various reports of corneal thinning, perforation and ulceration due to abuse of topical anesthetics.[16]

NSAIDs

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used against ocular inflammation that is triggered due to diseases such as allergic conjunctivitis, and in the long term management of cystoid macular edema post cataract surgery. NSAIDs when used over longer periods tend to hamper corneal epithelial cell turn over causing corneal melts which though rare is one of the most serious consequences. The deleterious effect of the NSAIDs is exacerbated by previous existing tear film instability and systemic diseases like diabetes, hence their use post cataract surgery must be supported by adequate ocular surface stabilization.

Medications for red eye

Multiple medications containing phenylephrine or naphazoline are household names for the treatment of a red eye commonly due to some minor irritation and allergy. These may be prescribed by the local chemist and non-healthcare professionals as well, and act by vasoconstriction and reducing the ocular surface blood flow. Prolonged use of these vasoconstrictors also causes a block in the protective inflammatory mediators to the surface. These are also known to cause CNS depression in infants and when left in their reach can have serious consequences

Corneal deposits

In our country the inadvertent use of topical antibiotics is exacerbated by the easy availability without the need for an evaluation by the ophthalmologist. Most used are the fluroquinalones amongst which ciprofloxacin is known to cause corneal deposits. Surface inflammation associated with an epithelial defect and instability in the surface tear film lead to crystallization of the drug compound on the surface forming deposits. The early phase is usually reversible with stopping the offending agent, but chronic conditions may need a mechanical scraping or a phototherapeutic keratectomy.

Effect of systemic medication

Anti-depressants

According to National Mental Health Survey of India in 2015-16, one in every twenty Indians are subject to depression.[17] One of the commonly prescribed anti-depressants Selective Serotonin Reuptake Inhibitors (SSRIs)[18] show the highest tendency towards development of (DED). SSRIs increases the levels of serotonin cause different ocular side effects specifically in tears that cause modulation of corneal nociceptor sensitization, reduced corneal nerve sensitivity, reflexes of lacrimal glands and tear film.[19] The use of SSRIs and TCAs particularly increase the propensity of dry eye disease as it decreases the secretions of the lacrimal glands that may manifest into photophobia [20]

Antipsychotics

Psychotropic drugs have been under researched with the aspect of having various ocular side effects due to drug toxicity and their effect on specific body mechanisms. These drugs have a potential to induce various adverse disorders which include keratoconjunctival issues, uveal tracts diseases, angle-closure glaucoma, cataract, retinopathy, depositions on cornea and various ocular surface side effects.[18] Clozapine used in the treatment of Schizophrenia reduces the activity of the lacrimal

glands and mucous secreting glands, and also causes morphological changes in the thickness of the cornea due to its anti-cholinergic and anti-dopaminergic effects.[21,22,23]

Chemotherapeutic drugs

Chemo therapeutic drugs have been an effective conventional treatment for cancer that is a global health issue leading to millions of deaths worldwide due abnormal and uncontrollable growth of cells within the body. The chemotherapeutic drugs act as cytotoxic agents that interfere with the cellular process of DNA synthesis and mitosis resulting in cell death and reduced tumor load.[24] *Clinically eye-lid scarring and dysfunction of meibomian glands due to different cytotoxic and inflammatory reactions of these drugs within the body has also been evidenced.*[25] *Chronic exposure to these drugs causes inflammation of mucosal membrane lining of the lacrimal system causing changes in the tear film.*[26] *In addition to this, for the anti-cancer treatment to cause ocular surface toxicity, the dosage, deliver system of the drug, duration of the treatment potentially affects the extent of toxicity, which sometimes also results in discontinuing the chemo therapeutic drug, contrastingly some studies gave no evidence of ocular toxicity due to dose response hence more research is required for investigation of ocular toxicities dependent on drug regimens.*[27]

Clinical features of disease

Ocular drug toxicity may present a very varied picture with multiple overlapping nonspecific signs and symptoms. Mild cases may present with a red inflamed eye whereas severe cases have more extensive involvement of the entire ocular surface from eyelid dermatitis, squamous blepharitis, chemosis and punctate keratitis to corneal ulceration and non-healing corneal epithelial defects

The three major causes of the reaction remain

a) Hypersensitivity: *allergic reaction to the active component/ preservative of the drug*

b) DED: *chronic use of the medication tends to cause instability in the composition of the tear film.*

c) Direct epithelial damage: *due to chronic and cumulative use of medication*

As discussed under the causative topical drugs the clinical picture is more often overlapping, with the most common complaint being a red eye, and significant increase in the conjunctival surface inflammatory mediators such as interleukins in most cases. Most of the symptoms can be attributed to damage and loss of the conjunctival and corneal surface goblet cells. Damage to the lacrimal functional unit due to many of the systemic drugs causes symptoms of dry eye disease with damage to the cell surface associated transmembrane mucins, which in turn has a detrimental effect of the ocular surface. Maintenance of an intact mucosal barrier is also important to maintain and adequate epithelial function, which when hampered causes superficial punctate keratitis and non-healing epithelial defects, and increased penetrance of the damaging compound.

Management

The management involves recognizing the problem, followed by the withdrawal of the agent which at times is difficult to pinpoint because of the multitude of the topicals being used. This is mostly seen when the diagnosis of the ocular ailment is unsure and a broader base therapy is prescribed, like in the case of infective keratitis where the exact causative microorganism is unknown.

The use of preservatives to prevent the contamination of the active drug compound needs to be considered and preservative free medications should be used for more chronic ailments like glaucoma.In some cases, the active compound itself may be causing a detrimental effect when used chronically and hence surgical intervention when appropriate may need to be considered

The management broadly involves breaking the cycle of surface inflammation by removing the inciting factor and adding mild surface acting topical steroids which in most cases provides immediate relief.

The DEWS committee has very well described targeted therapy for symptoms of dry eye disease based on the severity of symptoms. Mild cases respond to preservative free lubricants alone whereas the more severe cases may need more targeted therapy. Lid hygiene and warm compresses are important to manage the blepharitis component, and topical steroids to reduce the surface inflammation. The use of bandage contact lens for moderate to severe cases provides relief to the patient and helps in epithelial healing. Very severe cases with non-epithelizing defects may need amniotic membrane transplant and the use of systemic therapy as well.

The goal of management remains to restore the tear film and the ocular surface, the first step in which remains removing the inciting factor, and use of more targeted therapy rather than cocktail medications.

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