Ocular Surface Disorders and relation to Glaucoma

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Ocular surface disease is a common comorbidity finding in glaucoma patients. The diagnosisof ocular surface disease in the glaucomapatient is often overlooked because the focusof management is on the evaluation of IOP and on the markers of glaucomatous disease progression[1]. Simon et al noticed prevalence of OSD in 47.6% patients on topical antiglaucoma medication[2] and 60% OSD observed by Leung et al.[3] Topical antiglaucoma medication for duration of three months or more has been found to induce significant degree of subclinical inflammation, which has been detected as increase dexpression of HLA–DR on conjunctival epithelial cells[4]. Pro-inflammatory cytokine secretion by conjunctival cells occurs in response to topical treatment for glaucoma[5].

The major effects of topical anti-glaucoma medication and their preservatives on ocular surface includes ocal allergic reactions, chronic conjunctival inflammation, tear film abnormalities, corneal epitheliopathy, punctuate epitheliopathy, medically resistant herpetic keratitis, disruption of epithelial function, chronic inflammatory infiltration, expression of inflammatory markers, impaired wound healing, squamous metaplasia[6,7]. Adverse effects of antiglaucoma medication on ocular surface have been widely described. Effects could be attributed to the active component as well as to the preservative which further amplify toxicity[8]. Most commonly used antiglaucoma medications – timolol and latanoprost, when on chronic treatment can cause ocular surface changes. Timolol reduces tear production, probably by systemic and/or local effects of beta-adrenergic receptor blockade in the lacrimal and/or accessory palpebral glands. It is also known to inhibit proliferation of corneal epithelial cells[6,7].

Side effects may be related to preservative concentration, duration of use, and number of instillation[9]. However, preservatives are needed to preserve the sterility of ophthalmic formulations after multidose bottles are opened[10-12].

Benzalkonium chloride (BAC), a quaternary ammonium compound, is the most commonly used preservative in topical ophthalmic preparations. Its turnover is very slow and may be retained in the ocular tissues for as long as 168 hours after application[13]. BAC promotes the activation of lipooxygenases, synthesis and secretion of eicosanoids, inflammatory mediators and many cytokines such as interleukin (IL)-1a, tumor necrosis factor and IL-8 and IL-10, resulting in irritation, delayed hypersensibility and allergic reactions[14]. Delayed and prolonged effect of BAC is because of incorporation and persistence of BAC molecules in cell membranes[15]. Preservatives exert a detergent effect on the lipid layer of the tear film. This reduces its stability, causing it to evaporate more rapidly, and results in increased ocular dryness[16]. The impaired protective layer, predisposes the eye to inflammation and conjunctival metaplasia. In addition, preservatives have destructive effects on the mucous gland, reducing the number of goblet cells and production of the protective mucus layer[17]. The three mechanisms of BAC toxicity described include a detergent effect, causing loss oftear film stability, direct damage to the cornea and conjunctival epithelium and immune-allergic reaction[15].

Long-term use of topical antiglaucoma therapy, particularly combination treatment regimens has been associated with failure of glaucoma filtration surgery[9,16]. It has been shown that subconjunctival fibrosis develops because of increased fibroblast density in the subepithelial substantia propria, linked to an increase in inflammatory cells[9,12]. Immunohistochemical study of conjunctival and trabecular specimens from surgical patients treated with antiglaucoma eye drops has revealed significantly greater expression of fibroblastic and inflammatory markers in samples from patients who were receiving preserved

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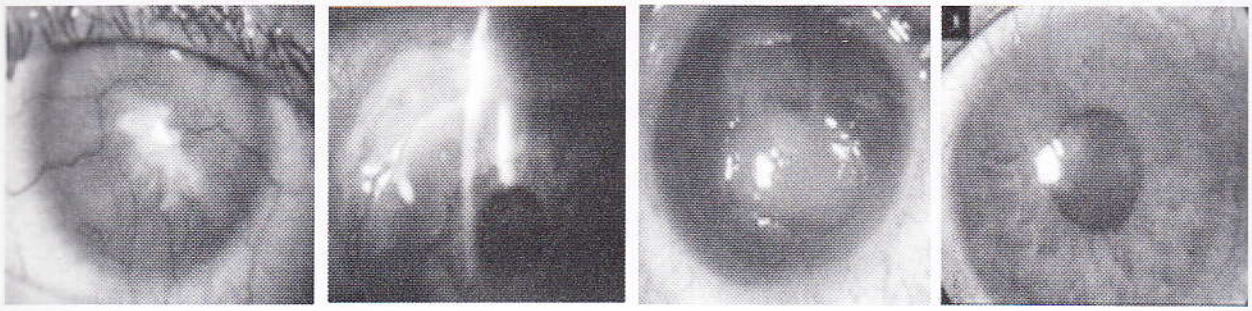
Expression of fibroblastic and inflammatory markers was seen to be higher in patients receiving polytherapy compared with those who were on monotherapy. Intensityof the inflammatory reaction seems related to the number ofpreservative-containing medications used and duration of treatment.

The innervation of the corneal epithelial cells and the stroma has an important influence in the corneal trophism and contributes to the maintenance of a healthy corneal surface1.The sub-basal nerve plexus along with stromal keratocytes secrete a number of neuro-peptides, which facilitate cell mitogenesis and migration, DNA synthesis, neurite extensionand survival, keratocyte proliferation and regulation of epithelialstem cells. Alterations in corneal innervations impairs the wound healing ability of the epithelium and results in dry eye.



The neuropeptides elaborated by corneal nerves influence corneal epithelial cells and these diffusible factors are believed to stimulate the epithelial growth, proliferation, differentiation and the production of collagen type VII16. The epithelial cells, in reciprocation, produce the soluble factors neuronal growthfactor (NGF) and glial cell-derived neurotrophic factor (GDNF)with a neurotrophic effect.

An alternative preservative to BAC is Purite®, a stabilized oxychloro complex (SOC). SOC consists of an equilibrium mixture of 99.5% chlorite, 0.5% chlorate, and trace amounts of chlorine dioxide. This preservative has been shown to have fungicidal, viricidal, and bactericidal activity. Although its exact mechanism of action has not beenfully elucidated, SOC oxidizes unsaturated lipids and glutathione in the cell and has proven antimicrobial efficacy. When SOC is instilled into the eye, it is converted into natural tear components: sodium and chloride ions, oxygen, and water. SofZia, the preservative used, is anoxidising complex containing borate, zinc and sorbitol, has less effect on human cells, which contain copious amounts of oxidases allowing the cells to withstand more oxidative stresses. Thus, ingeneral, oxidising preservatives are safe and effective at low concentrations while having less impact on the ocular surfaceof patients requiring chronic dosing of glaucoma medications.

Labbe A etal. compared toxicologicalprofile of BAC and Polyquaternium inexperimental study, found Compared toPQ-1, BAC consistently and dramatically altered the corneo-conjunctival surface as evaluated by slit-lamp examination, the fluorescein test, impression cytology, in-vivo confocal microscopy, and histology.

Concurrent use of topical cyclosporine to control ocular surface disease has been seen to be helpful in patients with chronic glaucoma who are on long-term usage of topical ocular hypotensive medications. A prospective comparative study done to evaluate changes in ocular surface after topical cyclosporine therapy, in chronic glaucoma patients on long-term topical antiglaucoma therapy has shown significant beneficial effects[16].This study evaluated the ocular surface evaluation of chronic glaucoma patientson long-term topical therapy treated concurrently with a topical cyclosporine 0.05% twice daily for 6 months compared to controls. The ocular surface evaluation tests, ocular surface disease (OSDI) indexscore (OSDI)), central corneal sensation were studied in these at recruitment and at the 6-month followup.

Schirmer's test, ocular surface staining scores, OSDI, corneal sensations, and corneal SBNFLD showed a statistically significant improvement following a 6-month concurrent topical CsA therapy in these patients.

Ocular surface needs to be evaluatedwith care in patients who are on long term anti-glaucoma therapy with consideration of use of concurrent topical cyclosporine to control the dry eye disease.

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