Chapter

Glaucoma and Dry Eye

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Abstract

Glaucoma treatment is closely related to the appearance or worsening of dry eye symptoms. The current topical treatment produces chronic inflammation that affects globet cells, meibomian glands and cornea, which translates into a decrease in the quantity and quality of the tear. It is characterized by increased osmolarity, which perpetuates damage to the ocular surface. Preservatives currently play a fundamental role in damage the ocular surface. There are numerous studies that have shown their toxic effects on the eye. Currently there are numerous preservative-free formulations and new therapies that allow us to improve the condition of the ocular surface in patients with glaucoma. A rational treatment is proposed using the different approaches available in the literature.

Keywords: Dry eye, Glaucoma, tear film, benzalkonium chloride

1. Introduction

Glaucoma is known to be a major cause of optic neuropathy that eventually leads to loss of vision. This is characterized by loss of retinal ganglion cells and their axons, excavated appearance of optic nerve head, and progressive loss of visual field sensitivities.

Quigley and colleagues published pooled-data analyses of glaucoma prevalence. In 2020, 80 millions of people are affected by glaucomatous optic neuropathy [1], of these, 60% will present concomitant ocular surface disease.

There is considerable evidence to suggest that medical treatment of glaucoma contributes to ocular surface disease (OSD) and the development of dry eye [2]; its prevalence with or without symptoms ranges from 5–50%, and the prevalence based on symptoms alone is very higher around 75% [3].

The cause of OSD in glaucoma patients is believed to be multifactorial and may include both the active component of the drug and the preservative, most commonly benzalkonium chloride (BAK), which is capable of causing inflammation and other anterior segment eye diseases that they range from allergy, blepharitis, dry eye, and anatomical eyelid abnormalities [3–5].

2. Mechanisms of damage

2.1 Inflammatory changes with topical treatment

The damage that occurs with topical treatment in glaucoma is the result of chronic inflammatory changes. A significant increase in macrophages, mast

cells and lymphocytes has been found in conjunctival biopsies, compared with biopsies of patients who have not received treatment. A significant increase in inflammatory markers has also been found, specifically IgE and Class II HLA-DR1 antigen. All of this suggests that topical treatment produces an inflammatory state on the ocular surface and even on the tenon. This was published in 1989 by Dr. Sherwood, he showed than this inflammatory state affects both the conjunctiva and the tenon [6]. Fibroblasts also were more prominent in the deeper conjunctiva and Tenon's capsule, this finding might be expected to enhance the risk of external bleb scarring after trabeculectomy or valve surgery. Also, this study, in patients who received long-term antiglaucomatous medical therapy, detected a significant decrease in the number of goblet cells in patients who received long-term antiglaucomatous medical therapy, this contributes to dry eye in glaucoma patients, in addition to other studies have explored the potential association between topical anti-glaucoma medications and meibomian gland dysfunction [7].

2.2 Meibomian gland dysfunction in Glaucoma

We know that Meibomian gland dysfunction (MGD) is a chronic diffuse eyelid margin disease that is associated with tear film instability, inflammation, and OSD. MGD is the most common cause of evaporative dry eye. The mechanism underlying the changes in the meibomian glands is unclear, some studies have reported that results by a chronic inflammation of the conjunctiva, altered by long-term anti-glaucoma eye drop use [6]. These chronic inflammation causes morphological and functional changes in the glands. Some studies have shown stagnation of meibum followed by the keratinization of orifices in the meibomian glands [8]. Arita et al., using non-contact meibography, compares a Two treated group with control, subgroup analysis revealed than the meibomian gland loss in the PG-treated eyes and β-blocker-treated eyes, that was significantly higher than in the corresponding controls [9].

2.3 Changes in extracellular matrix

In extracellular matrix (ECM) a pair of enzyme families called the matrix metalloproteinases (MMPs; a group of enzymes catalyzing the degradation of ECM) and the tissue inhibitors of metalloproteinase (TIMPs) are involved in the regulation and maintenance of the ECM. MMPs and TIMPs are involved in physiological mechanisms. ECM accumulation caused by changes of MMP and TIMP expression is significantly involved in the increased outflow resistance in glaucomatous eyes and changes in ECM metabolism of ocular surface tissue, specifically changes in conjunctival tissues, including a decrease in the number of epithelial goblet cells, and increase in subepithelial collagen deposition [10].

The topical treatment for glaucoma can cause damage to the ocular surface where different inflammatory pathways, which over time affect the globet cells and Meibomian glands among other ocular structures. This damage is due to both, the components of the drugs and the preservatives, of which the most used is BAK, However many studies indicate a direct correlation between the presence of preservatives and the symptoms experienced during antiglaucoma therapy. Most effects observed in glaucoma patients are therefore more likely to be due to the preservative than the active ingredients [11], however, It has been described specific alterations in the ocular surface from each family of drugs.

3. Clinical manifestation of specific medications on ocular surface

3.1 Prostaglandin analogs

Are the most powerful and efficient agents for controlling intraocular pressure among all current ocular hypotensive medications [12]. Latanoprost has been shown to induce squamous metaplasia, to stimulate HLA-DR overexpression at the conjunctival surface, and to cause significant changes in the metalloproteinase and tissue inhibitor balance [10, 13].

Conjunctival hyperemia is the earliest and most notorious side effect. The hyperemia is due to vasodilatation and not from an allergic reaction, as seen with other drug classes. This manifestation is more marked during the first month of use.

3.2 Beta-blockers

The Beta-blockers, for many physicians, is the second choice for controlling intraocular pressure, has been shown ocular discomfort due to burning, hyperemia, toxic keratopathy, superficial punctate keratopathy (SPK), periocular contact dermatitis, and dry eye [14].

SPK was the most common finding with surface staining. It was reported in 6% of patients using timolol.

Other reported effects of timolol is the decreases tear production. This effect is quantitatively limited and does not appear dangerous for normal eyes, although it may become so for eyes with an originally low lacrimal secretion [15].

3.3 α Adrenergic Agonists

Ocular surface the effects include ocular allergy, conjunctival follicles. Allergic reaction has been observed in up to 15% in chronic treatment with brimonidine [14].

3.4 Carbonic anhydrase inhibitors

Ocular surface side effects include allergic conjunctivitis and periorbital dermatitis [14].

4. The role of Benzalkonium chloride (BAK)

Benzalkonium chloride (BAK) has been used in ophthalmology since the 1940s. It is by far most common preservative, found in approximately 70% of eye drops while only 10% use other preservatives. It is used in different concentrations varied from 0.005% to 0.02% [16]. It is a quaternary ammonium compound that acts as a detergent, lysing cell membranes and thus killing microorganisms [17], in this way prevents bacterial and fungal contamination in multidose eye drop containers. It is highly effective as a preservative. It was also initially thought that the detergent effect of BAK might be necessary for the penetration of the active ingredient.

BAK toxicity for eye structures has been reported in many studies, in experimental or cell models have consistently and reliably shown its toxic effects. One major argument that is proposed to maintain the use of quaternary ammoniums in eyedrop formulations is that BAK reportedly enhances the penetration of the

drug into the anterior chamber, through disruption of the hydrophobic barrier of the corneal epitheliumm [18], however there are a large number of non-inferiority studies for bak free drugs that demonstrate the effectiveness of these medications.

4.1 Bak toxicity in globet cells

Low doses of BAK can induced proapoptotic efect on conjutival cells lines involving, as shown in vitro, reactive oxygen species and, therefore, oxidative stress reducing the number of goblet cells [19]. This cytotoxicity was proportional to the BAK concentration. In an interesting study by Guenoun, it was shown that these effects can be neutralized by topical prostaglandins analogs [20].

4.2 Corneal toxicity

Like the conjunctiva, the corneal cells have shown similar apoptotic response to BAK in superficial and deeper layers. Liang et al. confirmed the cytotoxicity of BAK in a model of a 3D culture of corneal epithelium. This study confirmed that BAK, depending on the time and concentration used, acts as a pro-inflammatory and pro-apoptotic agent able to impair the normal epithelium turnover irreversibly, even after BAK withdrawal [21].

Other study has been show topical application of BAK to the eye causes neurotoxicity, this secondarily produces reduction in aqueous tear production. Cessation of BAK treatment leads to resolution of inflammation, normalization of tear production, and recovery of stromal nerve density [22].

The damage to the ocular surface (conjuntiva, globet cells, Meibomian gland dysfunction and cornea) by topical treatment manifests itself with dry eye symptoms that have been described more frequently with the use of BAK. Jaenen et al. show a very high Prevalence of symptoms in patients using preserved drops, with 43% discomfort upon instillation, 40% burning or stinging sensation, 31% foreign body sensation, 23% dry eyes, 21% tearing, and 18% itchy eyelids [11]. Clinical impairment of the tear film and a rapid decrease of goblet cell density were also demonstrated after starting treatment with preserved timolol [22]. Schirmer's test and break-up time were altered compared to the basal control already significantly in the first month of treatment ($P < 0.01$ and $P < 0.001$, respectively). Similarly, impression cytology showed a progressive decrease in goblet cell density also significant at the first month.

5. Tear production and surface staining

The alteration of glaucoma medications affect the globet cells and meibomian glands affecting the tear film, both in quantity and quality [23]. This is accompanied by increased osmolarity.

Hyperosmolarity stimulates a cascade of inflammatory events in the epithelial surface cells, involving MAP kinases and NFkB signaling pathways and the generation of inflammatory cytokines (IL-1A; -1B; TNF-A) and MMPs (MMP9), which arise from or activate inflammatory cells at the ocular surface, these inflammatory events lead to apoptotic death of surface epithelial cells, including goblet cells, as already explained. In this way, a vicious circle is created that began with the topical treatment and is perpetuated over time. Clearly there are other factors such as the existence of previous ocular surface disease and individual variability that can give a wide range of symptoms [24].

6. Management of ocular surface disease in patient with Glaucoma: general perspective

Currently there are numerous bak-free drugs, laser therapy and minimally Invasive Glaucoma Surgery (MIGS) that help us in the management of the ocular surface and also improve adherence to therapy. The adherence and persistence is a problem, between 30 to 70% of patients do not comply with the indications in the management of glaucoma [25], in large part it is due to the irritative symptoms that these eyedrops produce.

Gupta et al. in his study shows that 90% of patients do not instillate the Eye drop properly [26]. The new advances in glaucoma therapy are focused on improving adherence and persistence with the aim of preserving the ocular surface and slowing the progression of the disease.

The bak-free medicine maintains an antimicrobial environment in a multidose container while minimizing toxicity to the ocular surface. The major disadvantage of preservative-free therapy is its cost and the handling of these containers, is often difficult for patients squeze the bottle, many of them have double chambers that avoid microbial contamination.

Selective laser trabeculoplasty (SLT) reduces intraocular pressure by increasing aqueous outflow through the trabecular meshwork with a single, painless outpatient laser procedure, minimal recovery time, and good safety profile. The Light study found that 74% of patients randomized to initial SLT remained drop-free at 36 months, suggesting that SLT is a particularly effective treatment in treatment-naïve patients [27].

MIGS have been developed as safer and less traumatic surgical interventions for patients with mild to moderate glaucoma or who are intolerant to standard medical therapy. It is an excellent option to avoid the use of topical medications. The problem of the MIGS continues to be accessibility; the high costs make them often prohibitive as a therapeutic option in developing countries.

Intense pulsed light therapy (IPL) is a promising complementary treatment for dry eye disease, specifically when dry eye syndrome is associated with skin disorders. Recent studies demonstrated in patients suffering from meibomian gland dysfunction (MGD), IPL therapy also reduces signs and symptoms of ocular surface disease [28]. The biological basis of this process is not well understood. The mechanism of action is by photomodulation that induces intracellular changes at the ducts of meibomian glands. There are no conclusive studies of its exact utility in patients with dry eye and glaucoma, however it may be a tool to consider [29].

6.1 Management of ocular surface disease in patient with Glaucoma

The classic management of glaucoma must be relationated with the Ocular surface evaluation. It's known the low % of glaucoma eye drops adherence. Recognize and make objective evaluations of the ocular surface can provide vital information about our patients. It can help to stratify the initial baseline therapy, and propose a double objective. Achieve the target IOP and the best Ocular surface condition in all patients.

There are two complementary forms of evaluate the ocular surface condition; Subjective, using validated questionnaires. These test evaluate the symptoms and how the patients confront the environment with the disease. Objective methods, is a standardized test to evaluate the cornea and conjunctival epithelium, and the tear film osmolarity.

- Subjective evaluation

  Validated questionaries

- Objective evaluation

  a. Ocular vital tinctions

  b. Osmolarity

     ○ Tearlab

     ○ Ipen

  c. Inflamation marker

  d. No contact measurements

     ○ Lacrydiag

     ○ Keratograph

6.2 Subjective evaluation: questionnaires

6.2.1 Ocular surface disease index (OSDI)

The OSDI test evaluates the symptoms provided by the patient and the function affection related to vision [30]. This 12-item questionnaire assesses dry eye symptoms and the effects it has on vision-related function in the past week of the patient's life [31]. The questionnaire has 3 subscales: ocular symptoms, vision-related function, and environmental triggers. Different Scores are provided related to the severity of ocular surface disease [32].

6.2.2 Standard patient evaluation of eye dryness questionnaire (SPEED)

The SPEED questionnaire was designed to make a rapid evaluation of dry eye symptoms [33]. It assesses whether these symptoms were not problematic, tolerable, uncomfortable, bothersome, or intolerable [34]. Also monitored diurnal and symptoms changes over 3 months [35]. The sensitivity and specificity of SPEED test versus OSDI were 0.90 and 0.80 respectively [35].

6.2.3 DEQ 5

The DEQ-5 consists of five questions that assess discomfort and dryness intensity. The overall DEQ-5 was calculated by summing the score on the individual questions. The reliability of the overall OSDI and DEQ-5 scores were 0.919 and 0.819 respectively [36].

6.3 Objetive measurements

6.3.1 Schirmer test (ST)

The Shirmer Test 1 (ST-1) is performed without instilling proparacaine i.e. topical anesthetic (reflex tear secretion), ST-2 after instilling proparacaine (basic tear secretion).

6.3.2 Non invasive tear break up time

The stained cornea is examined under the slit lamp in cobalt blue filter, the observer evaluate the appearance of first dry spot on cornea in less than 10 seconds. If this event occurs, its indicative of evaporative dry eye [37].

6.3.3 Ocular surface punctate staining

The observar stained cornea with fluorescein sodium and conjunctiva with lissamine green. Appearance of >5 corneal spots or > 9 conjuntival spot and lid margin (2 mm length & 25% width) seen under cobalt blue light is indicative of dry eye [37].

6.4 Osmolarity

6.4.1 Tear lab osmometer

Osmolarity testing has been declared the "gold standard" of objective dry eye diagnosis. Cutoff value >308 mOsm is indicative of hiperosmolarity state, and compatible with dry eye.

6.4.2 IPEN

The cut off value of 318 mOsm/L showed a sensitivity of 90.9% and specificity of 90.6% for diagnosing DED. The IPen osmometer can be considered suitable for use in the clinical setting, with good performance in DED diagnosis [38].

6.5 Inflamation test

INFLAMMADRY: Inflamma Dry is a rapid, in-office test that detects elevated levels of MMP-9, an inflammatory marker which is consistently elevated in the tears of patients with DED [39].

6.6 No contact evaluation

There are new devices at our disposal, which can evaluate and perform an adequate evaluation of the ocular surface. We explain two of them (No commercial interest). With these reports, the physician can explain an show the different characteristics altered in the test. This unique feature can improve the adherence to treatment.

- **Lacrydiag (Quantel)** [40] Reports available.
  - NIBUT (No invasive brake up time).
  - Lacrimal meniscus height.
  - LIPID LAYER INTERFEROMETRY - Measures lipid layer thickness and accurately diagnoses and monitors lipid-deficient tear.
  - MEIBOGRAPHY: Specialized imaging study developed exclusively for the purpose of directly visualizing the morphology of meibomian gland, they play a significant role in tear production by contributing lipids to the superficial tear film and hence dysfunction of the meibomian glands results EDE.

- **Keratograph** (Oculus) [41] Reports available.
  - NIBUT.
  - Lacrimal meniscus height.
  - LIPID LAYER INTERFEROMETRY - Measures lipid layer thickness and accurately diagnoses and monitors lipid-deficient.
  - MEIBOGRAPHY: Specialized imaging study developed exclusively for the purpose of directly visualizing the morphology of meibomian gland, they play a significant role in tear production by contributing lipids to the superficial tear film and hence dysfunction of the meibomian glands results EDE.

Management proposal

Once the glaucoma is diagnosed or we evaluate our patients in control, and recognize subjective or objective symptoms or signs, an escalated treatment is proposed. Our goal is **provide an adequate treatment, looking for no glaucoma progression with the minimal or none ocular discomfort.**

7. Treatment

Before initiating treatment, a careful evaluation of the ocular surface and periocular structures is mandatory. Its importan observe if any other alterations of the periocular structures are compromised, in example: lid malposition, rosacea, blepharitis, allergies, among the important. These alterations must me treated aiming to relieve the ocular surface [42]. In presence of early signs or symptoms of OSD are recognized (scores and/or objective evaluations), treatment must be initiated.

7.1 Evaluation of glaucoma treatment

As a general principle, the physician must evaluate, if it is possible, to:

1. Suspend Bak preservatives eyedrops
2. Promote use combined presentations
3. Evaluate use of SLT as initial treatment or MIGS.

7.2 Ocular surface management: basic treatment

7.2.1 Non preserved eyedrops

Cochrane reviews reports no difference in OTC (over the counter) artificial tears [43]. Preserved agents use alternative preservatives to BAK and may be considered because of the decreased cost, increased availability, and the convenience of standard multi-dose containers, non-preserved agents are preferred and should be considered wherever possible [44].

7.2.2 Heating devices

External eyelid heating devices have demonstrated efficacy in reducing surface staining scoring, improving TBUT and meibomian gland secretions, optimally with continued 2 times per day applications of ≥5 minútese [45, 46].

7.2.3 Eyelid hygiene

Its recommended by the authors, it must be evaluated the presence of Demodex or signs of rosacea. There are diverse options for treatment. Some products containing tree tea oil [52].

7.2.4 Omega 3 fatty acid supplementation

Omega-3 fatty acid supplementation significantly improved OSD symptoms and signs [47].

7.2.5 Lipidic substitutes eyedrops

Is used when a lipid deficiency is detectected, (Rosacea), meibomian gland disfunction. They are developed to enhance the lipidic layer of the tear-film, by different substances. Comercial eyedrops available are Systaine Balance and Optive Advance (no commercial interest) [48].

7.3 Ocular surface advance treatment

Ciclosporine % (Restasis) [49]:
Cochrane: studies support the topical CsA may increase the number of conjunctival goblet cells- FDA Approved

- Indication: Dry eye moderate
- Dosage: BID

Lifetigrast 5% (Xidra) [50]:

- Indication Dry eye FDA Approved
- Dosage: BID

Serum tears: [51].

- Indication: Second line, dry eye management.
  Different concentrations, usually 20%.
  Cochrane revision: no sufficient information.
- Dosage: QUID

7.4 Ocular surface estabilization

Other authors recommend suspend the topical glaucoma treatment and use topical steroids to evaluate the reincorporation of treatment and provide oral acetazolamide for the IOP control.

7.5 Local antinflamatory measures

7.5.1 Tea oil tree eyelid

- Indication: eyelid irritation Demodex follicullorum, demodex brevis
- Dosage: nocturnal use [52].

7.5.2 External eyelid brush

- Indication: Moderate Dry eye. Blepharitis, rosácea, Meibomian gland dysfunction.

- Dosage: 1 time/week [53].

7.5.3 Infrared pulse light (IPL)

- Indication: Moderate Dry eye. Blepharitis, rosácea, Meibomian gland dysfunction.

- Dosage: Different schedules provided by the manufacturer [29].

7.6 Surgery

It must be indicated as the first therapy, which depends of the conjunctival damage and glaucoma severity. This point is still on debate in the actual literature.

8. Author's recommendation

- Consider initiating preservative free topical medications or surgical/procedural alternatives such as laser trabeculoplasty, minimally invasive glaucoma surgery, or novel forms of drug delivery in all cases where possible and even more, if there is a previous ocular surface disease present.

- In all patients with maximum tolerated medical therapy, it is ideal to indicate eyelid cleanliness.

- Maximizing the health of the ocular surface may be another treatment option that is viable for some patients. Utilizing artificial tears with sodium hyaluronate or hydroxypropyl-methycellulose/dextran, both ocular surface lubricants, can provide some relief of ocular surface disease symptoms.

- In patients with an allergy reaction to different families of topical medications, it must be considered that there may be an allergic reaction to BAK.

- The reduction of irritative symptoms when switching to therapy without bak, generally occurs after three months of use.

- Topical cyclosporine 0.05% twice daily in conjunction with glaucoma drops if another preventative and ocular surface modifying measure, specifically if the patient had a filtering surgery.

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