Volume 7 Issue 1 2012

Dry eye testing in glaucoma

Jonathan E. Moore[1,2] and C.B. Tara Moore[2]
[1]Cathedral Eye Clinic, University of Ulster, Belfast, Northern Ireland
[2]School of Biomedical Sciences, University of Ulster, Coleraine, Northern Ireland

Chronic topical therapeutic management of glaucoma has the potential to deleteriously alter an ocular surface if medication is given at a high enough concentration for a sufficiently long period of time. Some ocular surfaces such, as those accompanying dry eye disease, are more susceptible to the effects of benzalkonium chloride and other preservatives. This review highlights the importance of considering and carefully assessing the ocular surface for evidence of dry eye or other problems, with the aim of enabling clinical intervention to prevent or retard the deleterious effect and exacerbation of ocular surface disease by topical glaucoma medication.

Medical management of glaucoma

Glaucoma is a common condition usually affecting an older age group. The main treatment options for the condition involve topical medication, laser treatment or surgical intervention. Topical medications have well-recognized toxicity reactions associated with prolonged usage and it is well recognized that chronic topical therapy can potentially deleteriously affect subsequent glaucoma shunt surgery.[1] Many of the ocular surface reactions secondary to topical medication are in fact due to the drug's formulation, such as the preservative used, rather than the active drug component. Benzalkonium chloride (BAK), traditionally the most common preservative for all eye drops, has been shown to be highly toxic to conjunctival epithelial and goblet cells as evidenced through treatment of primary cultured conjunctival cells with BAK.[1] Additionally, prolonged treatment of the ocular surface with BAK-containing drops has been shown to result in up-regulation of inflammatory cytokines, adhesion factors, and destructive enzymes.[2,3] Recognition of this problem has prompted significant research, and efforts by pharmaceutical companies to enhance and improve biocompatibility of these formulations with the introduction of both single-dose preservative-free eye drops and preservatives non-toxic to mammalian cells. The long-term beneficial effects upon the ocular surface of some of these changes in drop formulation are still to be assessed.[4]

Dry eye syndrome affects the ocular surface and tear film

A healthy tear film and ocular surface constitutes a significant protective barrier against all forms of insult to the eye, which is therefore much less likely to suffer from any early deleterious effects induced by chronic topical medication.[5] The corollary, however, is that a deficient tear film and compromised ocular surface has a greatly reduced capacity to withstand any form of challenge or stress.[6] It is particularly important that clinicians prescribing and administering topical glaucoma medications are able to both test for and recognize pathologically altered ocular surfaces and dry eye states prior to instituting their definitive treatment plan.[7]

Dry eye syndrome is a recognized group of disorders that culminate in the production of common signs and symptoms affecting the ocular surface and tear film.[5] Ocular inflammation is one of the single most common

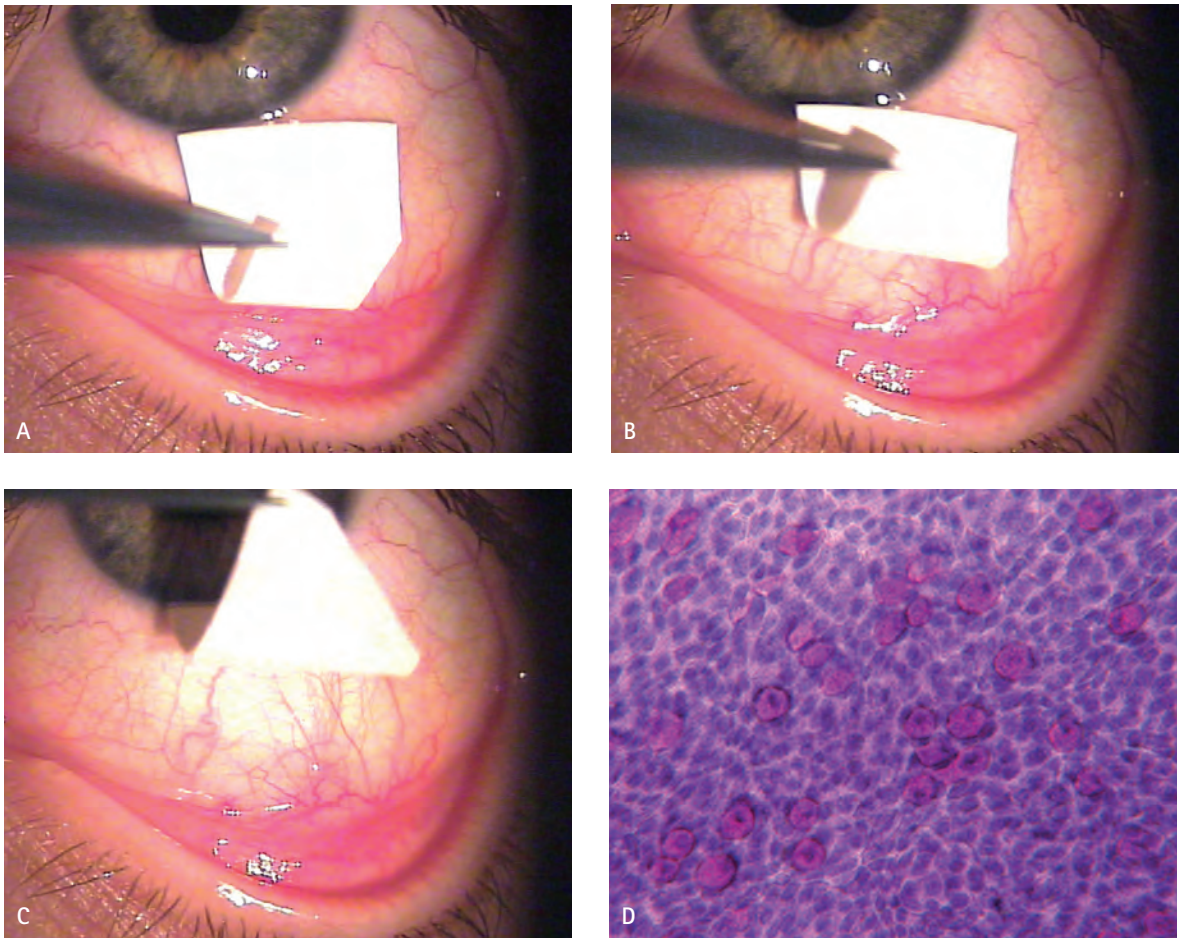

Figure. A–C: *Photographs showing impression cytology sampling of an eye.* ***D****: Photomicrograph of representative impression cytology specimen stained with periodic acid and Schiff reagent (PAS) to show goblet cells. This is representative of a normal cytological specimen post-PAS staining: the presence of goblet cells embedded in the epithelial sheet represented by the pink colour against conjunctival epithelia, counterstained purple with haematoxylin, with round-shaped epithelial cells, dense staining around the nuclei, and abundant goblet cells stained bright pink (original magnification, ×400).*

accompanying findings.[8] The term "ocular surface" recognizes the close interaction and interdependence of conjunctiva, cornea, lids, tears, and tear-producing glands.[9] Defects or damage to one of its components can rapidly spill over to affect the whole eye environment.[10]

As dry eye syndrome comprises a spectrum of disease severity, it is important that clinicians are able to recognize early evidence of disease or potential precipitating factors, in addition to more established disease. The tear film is traditionally regarded as a trilaminar structure comprising a predominantly aqueous layer overlying a mucous layer attached to the underlying epithelium and coated by an overlying lipid layer.[11] The regulation of the tear film is beyond the scope of this review but suffice to say there is evidence for regulation via both sensory and autonomic pathways,[12] and defects in either may contribute to disease states. The mucin layer is predominantly produced by goblet cells and has been shown to be affected early in dry eye disease,[13,14] which allows specialist clinics to grade dry eye disease based upon cytological examination of ocular surface impression cytology samples (Figure). Dry eye syndrome has been classically subdivided into aqueous deficiency and evaporative dry eye. However, both these types of

Table 1. Biomicroscopic grading of dry eye based on assessment of meibomian glands, lids, conjunctiva, and tear film debris.

Grading score	Meibomian glands	Lid and lid margin		Conjunctiva (palpebral and bulbar)	Tear film debris
		Erythema	Erythema/ Hyperaemia		
None (0)	No glands plugged	Normal	Normal	Absence of debris	
Mild (+1)	1–2 glands plugged	Redness localized to a small region of the lid margin or skin	Slight localized infection	Presence of debris in inferior tear meniscus	
Moderate (+2)	1–3 glands plugged	Redness of most or all lid margin or skin	Pink colour, confined to palpebral or bulbar conjunctiva	Presence of debris in inferior tear meniscus and in tear film overlying the cornea	
Severe (+3)	All 5 glands plugged	Redness of most or all lid margin and skin	Red colour of the palpebral and/or bulbar conjunctiva	Presence of debris in inferior tear meniscus and in tear film overlying the cornea. Presence of mucus strands in inferior fornix or on bulbar conjunctiva	
Very Severe (+4)		Marked diffuse redness of both lid margin and skin	Marked dark redness of the palpebral and/or bulbar conjunctiva	Presence of debris in inferior tear meniscus and in tear film overlying the cornea. Presence of numerous and/or adherent mucus strands in inferior fornix and on bulbar conjunctiva, or filamentary keratitis	

dry eye produce very similar signs and symptoms, and separation into two specific types is somewhat artificial, as finding one aspect in total isolation is highly unlikely due to the physiologically integrated ocular surface. The aim of clinical testing, however, has been to try, firstly, to diagnose the presence of dry eye and, secondly, to classify it if possible into one or another major subtype, in order to enable further specific treatments.[15]

Osmolarity testing

There is great variation in which diagnostic criteria[16] are currently used, and a significant problem faced by the clinician is that many of the tests used do not agree, and can even be at odds with each other. This problem is most prevalent in patients with mild-to-moderate dry eye,[17,18] while in more severe dry eye states the common clinical tests appear to concur well with each other. Several new diagnostic tools have started to enter the clinical arena and are helping to define specific aspects of the condition in more reproducible and effective ways. Osmolarity testing was initially proposed as a standard test at the First International Conference on the Lacrimal Gland, Tear Film, and Dry Eye in 1992.[19] Tear hyperosmolarity has been regarded as a central mechanism causing ocular surface inflammation, damage, and symptoms, and the initiation of compensatory events in dry eye.[5] The ease of testing tear osmolarity and the purported pathomechanistic role of hyperosmolarity in dry eye makes it an attractive prospect for positive diagnosis of the condition and it has been proposed as a possible biomarker for disease severity.[20,21]

Table 2. Potential sequence and types of tests to determine presence and severity of dry eye.	
Dry eye test sequence	**Tool or test used**
Questionnaire	Preclinical examination
Tear osmolarity	TearLab®
Tear meniscus	Slit lamp
Lid margin/meibomian glands	Slit lamp
Fluorescein tear film break-up time (FTBUT)	Slit lamp/fluorescein
Corneal/conjunctival staining	Slit lamp/fluorescein
Schirmer test	Schirmer paper

Defining a specific osmolarity number to correlate with or define mild dry eye is difficult. Based upon population studies, the manufacturers of the product have classified the mild dry eye spectrum commencing at 308–320 mOsmol/L. The range of 320–340 mOsmol/L has been classified as moderate dry eye, with anything greater being more severe. In early dry eye, fluctuation of osmolarity has also been described as early evidence of dry eye syndrome. There is significant elegance to this form of testing where a numerical factor can be used to define the severity of a condition. However, in mild-to-moderate disease, care should be taken prior to defining with certainty the diagnosis of dry eye without other confirmatory evidence.

Other diagnostic tools to detect presence and severity of dry eye symptoms

For clinicians, the key aspect required is to know which tests are both easy to carry out and effective in determining the presence, type, and severity of the condition. Several basic concepts already alluded to underpin the need for examination of the ocular surface for evidence of dry eye. Firstly, if dry eye is severe, all aspects of the ocular surface will be affected, inflammation will be apparent, and multiple dry eye tests will positively confirm the diagnosis.[15] In mild-to-moderate dry eye disease, inter-test concordance is often low,[15] and therefore it is important to perform combinations of tests, some of which are outlined in Tables 1 and 2, including assessment of symptoms, which is often best formalized through the use of specific

Currently no single test is suffcient to confidently define mild to moderate dry eye test should be confirmed by the evidence from another

questionnaires.[22] A general principle for accuracy in dry eye testing is that the less invasive tests should be carried out prior to the more invasive to reduce the likelihood of altering the underlying baseline state. Table 2 gives a reasonable stepwise test regimen to improve repeatability in results. Newer non-invasive interferometric techniques, together with topographic methods, have been developed to assess tear film thickness and stability.[23]

One of the principal aims of dry eye testing is to determine those patients at increased risk of inflammatory reactions to chronic glaucoma drop usage and to direct prophylactic management where appropriate to the patients on glaucoma medication. The recognition and management of structural lid abnormalities, treatment of atopy or meibomian gland dysfunction, replacement of aqueous tears, or management of overt inflammation can greatly enhance patient comfort and enable the continued tolerance of glaucoma medication, particularly in mild-to-moderate dry eye.[24]

Conclusion

The ocular surface can be deleteriously affected by treatment with long-term topical anti-glaucoma medication. Ophthalmologists should be proficient in detecting and managing dry eye and other ocular surface problems both before and after the introduction of antiglaucoma medication.

References

1. Cvenkel B, Kopitar AN, Ihan A. Correlation between filtering bleb morphology, expression of inflammatory marker HLA-DR by ocular surface, and outcome of trabeculectomy. J Glaucoma. [Epub ahead of print. 2011 Jul 5].
2. Mantelli F, Tranchina L, Lambiase A, et al. Ocular surface damage by ophthalmic compounds. Curr Opin Allergy Clin Immunol. 2011;11:464-70.

KEY MESSAGES

- Clinicians prescribing topical lenti-glaucoma medications should recognise pathologically altered ocular surfaces and dry eye states prior to instituting their definitive treatment plan.
- A general principle for accuarcy in dry eye testing is that the less invasive tests should be carried out prior to the more invasive to reduce the likelihood of perturbing the underlying baseline state.

3. Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010;29:312-34.
4. Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia-preserved topical glaucoma medications on human ocular epithelial cells. Adv Ther. 2010;27:837-45.
5. Gipson IK, Argüeso P, Beuerman R, et al. Research in dry eye: report of the Research Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:179-93.
6. Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011;28:267-82.
7. Monaco G, Cacioppo V, Consonni D, et al. Effects of osmoprotection on symptoms, ocular surface damage, and tear film modifications caused by glaucoma therapy. Eur J Ophthalmol. 2011;21:243-50.
8. Tavares F de P, Fernandes RS, Bernardes TF, et al. Dry eye disease. Semin Ophthalmol. 2010;25:84-93.
9. Thoft RA, Friend J, Kenyon KR. Ocular surface response to trauma. Int Ophthalmol Clin. 1979;19:111-31.
10. Paiva CS, Pflugfelder SC. Rationale for anti-inflammatory therapy in dry eye syndrome. Arq Bras Oftalmol. 2008;71(6 Suppl):89-95. Review.
11. Johnson ME, Murphy PJ. Changes in the tear film and ocular surface from dry eye syndrome. Prog Retin Eye Res. 2004;23:449-74.
12. Dartt DA. Neural regulation of lacrimal gland secretory processes: relevance in dry eye diseases. Prog Retin Eye Res. 2009;28:155-77. Review.
13. Albertsmeyer AC, Kakkassery V, Spurr-Michaud S, et al. Effect of pro-inflammatory mediators on membrane-associated mucins expressed by human ocular surface epithelial cells. Exp Eye Res. 2010;90:444-51.
14. Moore JE, Vasey GT, Dartt DA, et al. Effect of tear hyperosmolarity and signs of clinical ocular surface pathology upon conjunctival goblet cell function in the human ocular surface. Invest Ophthalmol Vis Sci. 2011;52:6174-80.
15. Moore JE, Graham JE, Goodall EA, et al. Concordance between common dry eye diagnostic tests. Br J Ophthalmol. 2009;93:66-72.
16. Lemp M, Baudoin C, Baum J, et al. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:75-92.
17. Goren MB, Goren SB. Diagnostic tests in patients with symptoms of keratoconjunctivitis sicca. Am J Ophthalmol. 1988;106:570-4.
18. Kallarackal GU, Ansari EA, Amos N, et al. A comparative study to assess the clinical use of Fluorescein Meniscus Time (FMT) with Tear Break up Time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. Eye (Lond). 2002;16:594-600.
19. Farris RL. Tear osmolarity: a new gold standard? Adv Exp Med Biol. 1994;350:495-503.
20. Suzuki M, Massingale ML, Ye F, et al. Tear osmolarity as a biomarker for dry eye disease severity. Invest Ophthalmol Vis Sci. 2010;51:4557-61.
21. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. Invest Ophthalmol Vis Sci. 2010;51:6125-30.
22. Gothwal VK, Pesudovs K, Wright TA, et al. McMonnies questionnaire: enhancing screening for dry eye syndromes with Rasch analysis. Invest Ophthalmol Vis Sci. 2010;51:1401-7.
23. Szczesna DH, Kasprzak HT, Jaronski J, et al. An interferometric method for the dynamic evaluation of the tear film. Acta Ophthalmol Scand. 2007;85:202-8.
24. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol. 2011;151:792-8.e1.