Ocular Surface Disease Exacerbated Glaucoma: Optimizing the Ocular Surface Improves Intraocular Pressure Control

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Purpose: To describe a series of 4 patients with inadequately controlled primary open angle glaucoma and ocular surface disease (OSD) in whom a combination approach was used to manage the OSD resulting in improved intraocular pressure (IOP) control.

Patients and Methods: A retrospective review of the clinical notes of 4 patients referred to a tertiary surgical glaucoma service was performed. At the initial visit, measures to control the OSD were employed in all patients; twice-daily lid hygiene measures, a 3-month course of 50 mg daily oral doxycycline, topical carmellose sodium (celluvisc) 0.5% 4 to 6 times daily, and preservative-free equivalents of topical antiglaucoma medications as deemed appropriate, depending on the perceived severity of the OSD.

Results: Patients were reviewed for a maximum of 24 months after intervention. In all patients treatment resulted in a marked symptomatic and clinical improvement in the ocular surface with a reduction in hyperemia, meibomian gland dysfunction and superficial keratopathy. A reduction in the IOP also occurred in all patients, obviating the need for glaucoma drainage surgery during the study period.

Conclusions: Patients with severe OSD often have glaucoma that is refractive to medical therapy. Furthermore, the surgical success of glaucoma filtering surgery is compromised in patients with scarring and inflammation of the conjunctiva. The term we postulate is "OSD exacerbated glaucoma." This is the first study to suggest that the use of a combination approach comprising medical treatment to manage the OSD in patients with primary open angle glaucoma may lead to an improvement in the IOP control and the management of glaucoma.

Key Words: glaucoma, ocular surface disease, ocular surface inflammation, preservative

(*J Glaucoma* 2014;23:56–60)

Ocular surface disease (OSD) is an umbrella term that includes dry eye, lid disease, conjunctivitis, and keratitis. OSD is highly prevalent in patients with glaucoma and ocular hypertension[1] and the severity of OSD symptoms increases with the number of medications used.[2] OSD causes significant morbidity[3] and has a negative impact on treatment compliance,[4] quality of life,[5] and surgical outcomes.[6]

The development of OSD in glaucoma patients has been attributed primarily to the use of benzalkonium chloride (BAK), the common preservative in antiglaucoma medications.[3] Evidence also suggests that the active component of the commonly used medications to treat glaucoma also has an effect on the ocular surface[7] as does the patient predisposition to the development of OSD.

We describe a series of patients, referred to our tertiary surgical glaucoma service, in which a combination approach was used to manage the OSD. The measures included changing the antiglaucoma medications to preservative-free preparations where appropriate and commencing oral doxycycline, topical lubricants, and lid hygiene measures. This resulted in improved intraocular pressure (IOP) control. To our knowledge, there are no published reports on the effect of this type of approach on the control of IOP.

MATERIALS AND METHODS

A retrospective review of the case notes of 4 National Health Service patients referred to our tertiary surgical glaucoma service in the West Midlands, United Kingdom in the years 2008 to 2012 with inadequately controlled primary open angle glaucoma was performed.

The initial assessment included a detailed ocular, systemic, and drug history and a thorough ocular examination including IOP assessment, anterior segment evaluation, gonioscopy, pachymetry, and dilated fundoscopy. Clinical details of the OSD were documented for all patients.

In all 4 patients, treatment for the OSD was prescribed at the first visit. Lid hygiene comprising twice-daily lid margin massage using a hot moist face towel was discussed with all patients. A 3-month course of oral doxycycline, 50 mg once daily was prescribed. Topical carmellose sodium (celluvisc) 0.5% to be used 4 to 6 times daily was prescribed for continued use. Topical antiglaucoma medication was changed to preservative-free equivalents as appropriate, depending on the perceived severity of the OSD as judged by the examining consultant ophthalmologist. All patients were reviewed at 3 months and then as clinically required.

RESULTS

The patient demographics, ocular, medical, and drug history (prescription and nonprescription medication) and examination findings at the time of referral to the specialist glaucoma service are outlined in Table 1. The IOPs pre-referral, at referral, and after intervention are documented in Table 2 along with the nature of the intervention to control the OSD.

All of the patients reported good compliance with their glaucoma treatment before referral to the glaucoma service. All 4 patients experienced ocular discomfort at the initial assessment. There was marked symptomatic and clinical improvement in the ocular surface after treatment. A reduction in hyperemia, meibomian gland dysfunction, and superficial keratopathy was documented for all patients.

Patients were reviewed for a maximum of 24 months after intervention. Neither was there any deterioration in

Received for publication September 7, 2011; accepted June 5, 2012.
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Disclosure: The authors declare no conflict of interest.
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TABLE 1. Description of Cases 1 to 4

Case	Age (y)	Sex	Years Since Diagnosis	Past Ocular History	Past Medical History	Drug History	IOP Treatment	Visual Fields	BCVA	Anterior Segment	Gonioscopy	C:D Ratio	CCT (μm)
1	79	Male	8	Bilateral pseudophakia Left epimacular membrane	Nil	Nil	g. latanoprost nocte R + L g. timolol + dorzolamide combination BD R + L	R full L inferior arcuate scotoma	R 6/9 L 6/12	MGD Hyperemia Papillae PEEs Decreased MTS and TBUT	Open angles	R 0.4 L 0.9	R 524 L 522
2	82	Female	11	High myope R ECCE + IOL R CNVM	Type 2 diabetes Hypertension Pacemaker	Amlodipine Gliclazide Aspirin	g. brinzolamide BD R + L g. brimonidine + g.timolol combination BD R + L g. bimatoprost 0.03% nocte R + L	R + L Superior arcuate scotoma	R 2/60 L 6/12	MGD Hyperemia Mild subtarsal scarring Papillae PEEs Decreased MTS and TBUT	Open angles	R 0.95 L 0.95	R 522 L 509
3	77	Female	5	Nil	Nil	Nil	g. bimatoprost + g. timolol combination OD R + L g. brinzolamide BD R + L		R 6/9 L 6/9	MGD Hyperemia PEEs Decreased MTS and TBUT	Open angles	R 0.8 L 0.95	R 532 L 521
4	80	Female	> 14	Nil	Nil	Nil	g. latanoprost nocte R + L g. brinzolamide BD R + L g. brimonidine 0.1% BD R + L	R + L nasal step	R 6/6 L 6/9	Anterior blepharitis MGD Conjunctival scarring Papillae PEEs Decreased MTS and TBUT	Open angles	R 0.6 L 0.7	R 487 L 489

BCVA indicates best corrected visual acuity; BD, twice daily; C:D ratio, optic cup-to-disc ratio; CCT, central corneal thickness and intraocular lens; CNVM, choroidal neovascular membrane; ECCE + IOL, extra capsular cataract extraction; L, left; MGD, meibomian gland dysfunction; MTS, marginal tear film strip; OD, once daily; PEEs, punctate epithelial erosions; R, right; TBUT, tear break-up time.

TABLE 2. Details of Intervention and Intraocular Pressures

Case	Range of IOPs 1 y Before Referral (mm Hg)	Highest Recorded IOP	IOP at Presentation to Tertiary Glaucoma Clinic (mm Hg)	Intervention	Posttreatment IOP (mm Hg) at No. Months (mo) After Intervention			
1	R 15-20 L 15-20	R 28 on August 19, 2002 L 42 on October 19, 2001	R 14 L 19	Hot compress BD Punctal plugs g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo g. timolol + dorzolamide combination preservative-free BD both eyes g. latanoprost nocte both eyes (as before)	R 13 L 13 3 mo	R 10 L 11 8 mo	R 8 L 11 14 mo	R 9 L 9 19 mo
2	R 24-30 L 24-28	R 26 on April 23, 2002 L 28 on May 6, 2008	R 24 L 24	Hot compress BD g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo Left cataract surgery Glaucoma medication unchanged	R 16 L 16 3 mo	R 14 L 10 9 mo	R 15 L 14 17 mo	
3	Unknown	Unknown	R 20 L 19	Hot compress BD g. celluvisc 0.5% 4-6 × per day Doxycycline 50 mg OD 3 mo g. bimatoprost nocte R + L g. timolol 0.5% preservative-free BD R + L g. dorzolamide preservative-free BD R + L	R 12 L 13 3 mo	R 12 L 12 8 mo	R 15 L 15 12 mo	
4	R 16-30 L 16-26	R 34 L 36 On April 8, 2002	R 30 L 20	Hot compress BD g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo g. timolol + dorzolamide combination preservative-free BD both eyes g. travoprost BAK-free nocte R + L	R 18 L 18 2 mo			

BAK indicates benzalkonium chloride; BD, twice daily; IOP, intraocular pressure; OD, once daily.

the field of vision nor any change in the appearance of the optic disc in any of the patients during the study period. No changes were made to the topical glaucoma medications after the initial intervention. None of the patients reported any change in their systemic health or medication during the reported period.

DISCUSSION

OSD and glaucoma frequently coexist. The long-term use of topical antiglaucoma medication has been shown to cause OSD and can lead to conjunctival inflammation, foreshortening, and shrinkage.[8] Severe symptomatic cicatrization may subsequently develop, which is clinically and pathologically indistinguishable from ocular cicatricial pemphigoid (OCP) and has been referred to in the literature as drug-induced cicatricial conjunctivitis and pseudopemphigoid.[9]

It is also true that glaucoma is more prevalent in patients with OSD. Tsai et al,[10] found the prevalence of glaucoma in patients with severe OSD to be 65.7%. In another study, Tauber et al[11] theorized the possible mechanisms of raised IOP in OSD. They found significantly increased conjunctival inflammation in patients with OCP using antiglaucoma medications, as compared with patients with OCP but without glaucoma, suggesting that antiglaucoma medications continue to initiate or provoke inflammation. Furthermore, the changes in the ocular tissues that occur as a result of OCP may promote the development of elevated IOP. The authors postulated that the mechanism for the elevated IOP may be related to vascular etiologies and inflammation of the trabecular meshwork. Inflammation and scarring of the episclera and sclera may further impair the outflow facility of the eye.[11]

All of our patients had previously unrecognized clinical signs and symptoms of OSD in addition to inadequately controlled IOP. Surgical options in this setting would likely result in a suboptimal outcome, hence a combination approach was used to treat the OSD. Twice-daily lid hygiene using a hot compress, topical lubricants, and oral doxycycline were used. In some cases, the antiglaucoma treatments were changed to preservative-free equivalents as appropriate. The rationale for this approach is explained below.

Topical preservative-free lubrication used regularly has been shown to improve ocular surface health[12] and the use of hot compresses to the eyelids in addition to lid massage anecdotally improves meibomian gland function and may improve ocular surface blood flow.

BAK, the common preservative in antiglaucoma medications, is reported to produce severe changes in epithelial cells, including loss of microvilli, disruption of plasma membranes, and desquamation of the top 2 layers of cells.[13] Glaucoma medications containing higher concentrations of BAK result in greater damage to the cornea and conjunctiva compared with preparations preserved with lower concentrations of BAK. Reducing BAK exposure by switching from preserved to preservative-free medication or reducing the number of eye drops containing BAK leads to a significant reduction in the clinical signs of OSD.[14]

Henry et al[15] evaluated the effect of changing to preservative-free g. travaprost 0.004% from prior use of preserved prostaglandin therapy with either g. latanoprost

0.005% or bimatoprost 0.03%. The study concluded that not only was there a clinically and statistically significant improvement in OSD symptoms and signs but there was also a statistically significant reduction in the mean IOP ($P < 0.0001$). This study, however, was not carried out in a parallel, randomized masked fashion.[15]

In a study of the conjunctival and trabecular meshwork changes in patients with glaucoma undergoing trabeculectomy, Baudouin et al[16] reported a higher rate of inflammatory cell infiltrates and fibroblasts in tissue samples from patients exposed to chronic preserved glaucoma medications than samples from those exposed to monotherapy or patients who underwent primary surgery. They concluded that BAK-preserved medications may cause inflammatory changes in conjunctival and trabecular tissues. This finding can be used to support the aforementioned theory that the elevated IOP in patients with OSD is secondary to inflammation of the trabecular meshwork.[16]

It is also recognized that preservative increases the penetration of topical treatment by having a detrimental effect on the ocular surface. de Jong et al[17] found that the corneal permeability decreased significantly (mean decrease per patient 27%; $P = 0.025$) in patients who switched from treatment with timolol preserved with BAK to preservative-free timolol. Discontinuing preserved treatment and commencing nonpreserved treatment would be expected to reduce the penetration of the active agent and therefore lead to a reduction in the IOP-lowering effect. The observed improvement in the IOP-lowering effect in our patients is perhaps somewhat surprising but we postulate that it is secondary to decreased inflammation of the trabecular meshwork, conjunctiva, episclera, and sclera leading to improved outflow facility of the eye. Perhaps a healthy ocular surface is more important than increased penetration of glaucoma medications in some patients.

Doxycycline, a broad-spectrum tetracycline antibiotic, is an established treatment for OSD. Tetracyclines exhibit multiple anti-inflammatory properties and have been used to treat numerous inflammatory conditions including rheumatoid arthritis. Tissue culture studies have demonstrated that the mechanism of anti-inflammatory action is the inhibition of T-cell activation and chemotaxis, the downregulation of proinflammatory cytokines, including tumor necrosis factor-α and interleukin-1β, and the inhibition of matrix metalloproteinases that have been pathologically activated.[18] In addition, doxycycline may also kill migratory keratocytes or fibroblasts responsible for the formation of scar tissue, promote complete coverage of the ocular surface with epithelial basal cells, and consequently lead to the development of a stable, stratified epithelium.[19]

It seems that glaucoma therapy causes OSD and that severe OSD in turn exacerbates glaucoma. The aim of our treatment approach was to break the destructive cycle of events and achieve improved IOP control and a healthy ocular surface.

In all 4 cases an improvement in the OSD resulted in an improvement in the IOP control. The reduction in the IOP obviated the need for surgical intervention, during the study period. If glaucoma filtration surgery is subsequently required, the improvement in the ocular surface may contribute to the increased likelihood of a successful surgical outcome. It is also pleasing to note the sustained control of the IOP and stabilization of the visual field that has resulted from this approach, which suggests that a healthy ocular surface helps in the medical control of glaucoma in the longer term.

It can be argued that in our patients the reduction in IOP may have been due to improved compliance with treatment for 2 reasons. Firstly, care was transferred from a general clinic setting to a specialist consultant-led glaucoma service and hence increased emphasis was placed on the severity of the glaucoma, its implications on the quality of life and the possibility that surgical intervention would be required. Secondly, the reduction in ocular discomfort due to treatment of the OSD may have resulted in improved compliance. All 4 patients did, however, report good compliance with treatment before being referred to the surgical glaucoma service and the longer term control of IOP suggests that poor compliance was not the main issue in these patients.

The shortcomings of this study are that it is a retrospective chart review and clinic-based observation capturing uncontrolled and highly variable IOP endpoints. The sample size is small and follow-up period is limited. Although it can be argued that the IOP data are therefore of limited value, the longer term stabilization of disease based on visual field data, however, does suggest that our approach may be beneficial in managing this group of patients. This series provides a level of evidence in an area of importance where little clinical material currently exists. A need for larger, more robust randomized studies to test our hypothesis on this subject is apparent.

It is evident that patients with severe OSD often have glaucoma that is refractive to medical therapy because of the aforementioned factors and also to subacute and chronic scarring.[10] Furthermore, the surgical success of glaucoma filtering surgery is compromised in patients with scarring and inflammation of the conjunctiva secondary to preoperative long-term and combination use of topical antiglaucoma medications.[20] For these reasons the management of such patients can be challenging.

Our study, therefore, raises a new argument for maintaining increased awareness of the signs and symptoms of OSD in patients with glaucoma and the importance of timely diagnosis and treatment of the condition. The diagnosis and adequate treatment of OSD in the glaucoma population requires clinical awareness, diagnostic skill, and knowledge of the various treatment options. This can be difficult to achieve in high volume glaucoma clinics.

We suggest that in medically treated glaucoma patients, consideration should be given to the thorough assessment and treatment of OSD including use of preservative-free lubricants and antiglaucoma medication as these measures may improve glaucoma management, which may contribute to reducing the effects of long-term glaucoma complications.

We suggest that this phenomenon be known as "OSD exacerbated glaucoma."

REFERENCES

1. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. *J Glaucoma.* 2008;17:350–355.
2. Fechtner RD, Godfrey DG, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea.* 2010;29:618–621.
3. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol.* 2002;86:418–423.
4. Chawla A, McGalliard JN, Batterbury M. Use of eye drops in glaucoma: how can we help to reduce non-compliance? *Acta Ophthalmol Scand.* 2007;85:464.

5. Pouyeh B, Viteri E, Feuer W, et al. Impact on ocular surface symptoms on quality of life in a United States veterans affairs population. *Am J Ophthalmol.* 2012;153:1061–1066.
6. Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication II. The outcome of filtration surgery. *Arch Ophthalmol.* 1994;112:1446–1454.
7. Asbell PA, Potapova N. Effects of topical antiglaucoma medications on the ocular surface. *Ocul Surf.* 2005;3:27–40.
8. Schwab IR, Linberg JV, Gioia VM, et al. Foreshortening of the inferior conjunctival fornix associated with chronic glaucoma medications. *Ophthalmology.* 1992;99:197–202.
9. Liesegang TJ. Conjunctival changes associated with glaucoma therapy: implications for the external disease consultant and the treatment of glaucoma. *Cornea.* 1998;17:574–583.
10. Tsai JH, Derby E, Holland EJ, et al. Incidence and prevalence of glaucoma in severe ocular surface disease. *Cornea.* 2006;25:530–532.
11. Tauber J, Melamed A, Foster S. Glaucoma in patients with ocular cicatricial pemphigoid. *Ophthalmology.* 1989;96:33–37.
12. Sanchez MA, Torralbo-Jimenez P, Giron N, et al. Comparative analysis of carmellose 0.5% versus hyaluronate 0.15% in dry eye: a flow cytometric study. *Cornea.* 2010;29:167–171.
13. Sherwood MB, Grierson I, Millar L, et al. Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. *Ophthalmology.* 1989;96:327–335.
14. Jaenen N, Baudouin C, Pouliquen P, et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol.* 2007;17:341–349.
15. Henry JC, Peace JH, Stewart JA, et al. Efficacy, safety and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy. *Clin Ophthalmol.* 2008;2:613–621.
16. Baudouin C, Pisella PJ, Fillacier K, et al. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. *Ophthalmology.* 1999;106:556–563.
17. de Jong C, Stolwijk T, Kuppens E, et al. Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluoresence of the cornea in glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 1994;232:221–224.
18. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol.* 2006;54:258–265.
19. Smith VA, Cook SD. Doxycycline—a role in ocular surface repair. *Br J Ophthalmol.* 2004;88:619–625.
20. Lavin MJ, Wormald RP, Migdal CS, et al. The influence of prior therapy on the success on trabeculectomy. *Arch Ophthalmol.* 1990;108:1543–1548.

Erratum

Risk Factors for Visual Field Progression in the Groningen Longitudinal Glaucoma Study: A Comparison of Different Statistical Approaches: Erratum

There was an error in the Results section of the abstract and in the Results of the article. Below, please find the corrected passages of text.

Original Abstract Results:

With an additional stepwise selection procedure, mean IOP during follow-up (1.16 per mm Hg; 1.05-1.29; $P = 0.003$), baseline HFA mean deviation (MD; 2.72 for worse versus worse than −6 dB; 1.50-4.95; $P = 0.001$) and age (1.03; 1.01-1.06; $P = 0.010$) predicted progression.

Corrected Abstract Results:

With an additional stepwise selection procedure, mean IOP during follow-up (1.16 per mm Hg; 1.05-1.29; $P = 0.003$), baseline HFA mean deviation (MD; 2.72 for worse versus better than −6 dB; 1.50-4.95; $P = 0.001$) and age (1.03; 1.01-1.06; $P = 0.010$) predicted progression.

Original Results:

Applying a stepwise variable selection resulted in a model that had the HFA MD (OR 2.72 for better versus worse than −6 dB), mean IOP during follow-up (OR 1.16 per mm Hg increase) and age (OR 1.03) as independent risk factors for progression. With the EMGT and CGS approaches, three variables were found to be independent predictors of NPA progression. The FDT MD, baseline IOP and age increased the risk of NPA progression by 75% for better versus worse than −6 dB, 7% per mm Hg increase in baseline IOP and 3% per year of increase in age, respectively in both approaches.

Corrected Results:

Applying a stepwise variable selection resulted in a model that had the HFA MD (OR 2.72 for worse versus better than −6 dB), mean IOP during follow-up (OR 1.16 per mm Hg increase) and age (OR 1.03) as independent risk factors for progression. With the EMGT and CGS approaches, three variables were found to be independent predictors of NPA progression. The FDT MD, baseline IOP and age increased the risk of NPA progression by 75% for worse versus better than −6 dB, 7% per mm Hg increase in baseline IOP and 3% per year of increase in age, respectively in both approaches.