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Editorial

Ocular Hyperaemia in Glaucoma Patients Under Topical Intraocular Pressure Lowering Medication

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Abstract

Glaucoma remains one of the main burdens of preserving vision and vision related quality of life. Though probability of long-term preservation of vision has improved considerably in open-angle glaucoma for those who are diagnosed early and treated according to the modern glaucoma guidelines, the vision related quality of life may still be compromised by cosmetic effects and tolerance issues of the various topical glaucoma medications. Ocular hyperaemia remains the most common patient recognized problem of topical glaucoma medication. In order to avoid unnecessary patient anxiety and treatment cessation, understanding the reasons and types of ocular hyperaemia related to topical intraocular pressure lowering medication remains essential. The current Editorial gives an overview of the main types of medication induced ocular hyperaemia in glaucoma, and also guides the reader across actions, which are required from the managing ophthalmologist.

Keywords: *Glaucoma; Ocular Hyperaemia; Prostaglandin Analogue; Rho Kinase Inhibitor; Topical Glaucoma Medication*

Introduction

Glaucoma remains a main health problem for all regions in the World, since the prevalence of this disease group has increased significantly with ageing of the populations, and a further increase of glaucoma prevalence is projected for the upcoming decades [1]. While management of angle closure glaucoma requires surgical interventions, the open-angle glaucoma (OAG) forms are typically treated with topical intraocular pressure (IOP) lowering medications. This way of IOP lowering remains essential for most OAG patients on the long run, even if selective laser trabeculoplasty (SLT) and less invasive surgical IOP lowering modalities gain increasing role in the management.

Topical IOP lowering medication, however, is frequently associated with ocular surface redness (ocular hyperaemia) [2]. This may be disturbing for some patients. As a consequence, some patients may stop using their successful medication, which can lead to worsening of their glaucoma stage (disease progression). Others may suffer from serious side effects or allergy to some ingredients of their topical IOP lowering medication. These individuals need to stop using the causative eye drops. In order to help our patients an educated evaluation of the ocular hyperaemia type and the background mechanism is necessary, and an appropriate patient education by the treating ophthalmologist is required.

Main types of topical medication induced ocular hyperaemia in glaucoma

There are common and typical types of ocular hyperaemia which are related to topical glaucoma medication. It is important to note that all kinds of eye redness (e.g. redness due to infections, injuries, high IOP, uveitis) can also occur in OAG, but the hyperaemia forms discussed below are directly related to some ingredients or formulations of chronic IOP lowering medication [2].

The main types of ocular hyperaemia related to chronic topical glaucoma medications are:

- Toxic ocular surface disease (OSD).
- Allergy against an ingredient or a formulation of the eye drop.
- Passive venous dilation due to ingredients that dilate conjunctival veins.
- Passive episcleral veinous dilation due to ingredients that dilate episcleral veins and reduce episcleral venous pressure.

Toxic ocular surface disease in glaucoma

The most common form of OSD on topically treated glaucoma eyes is chronic, preservative induced toxic OSD. It is important to differentiate dry eye disease (DED) which reflects on insufficient tear film functions, and OSD which is an active inflammatory process. It is well-known that eye drop preservatives, in particular benzalkonium chloride (BAK), exert a dose dependent toxic effect on the ocular surface, and probably also on the trabecular meshwork. These effects increase with increasing quantity of BAK, in other words with instilling more preserved drops per days, and longer duration of BAK-preserved therapy. Since glaucoma is a chronic disease which is treated with drops for decades, glaucoma medication related OSD is common on those glaucoma patients who are treated with preserved IOP lowering eye drops [2,3].

OAG patients suffering from OSD complain about eye redness, dry eye feeling, difficulty in opening the eyes and sudden excessive tearing episodes. These complaints usually increase during the day. For them the only relief is cessation of the preserved topical therapy, and a change for a preservative-free eye drop option.

Allergy against an ingredient of the eye drop

Though an allergic reaction can develop against almost any eye drop ingredient, some IOP lowering drug classes are particularly commonly associated with severe local ocular allergies. The alpha receptor agonists (e.g. brimonidine) commonly induce both intolerance (pain, foreign body sensation and irritation feeling in the eyes with no major objective signs) and severe inflammation (toxic anterior segment reactions and subepithelial corneal infiltrates). The latter form typically requires a longer medication period before the onset, while the former form can rapidly appear either early in the treatment (even after the very first dose), or after a long uneventful period [4]. The effects can be triggered by both alpha receptor agonist monotherapy and fixed dose combination therapies containing an alpha agonist molecule, and can appear (though less commonly) when the eye drop versions are preservative free and/or contain lower alpha receptor agonist concentrations. It is important to note that elimination of the causative alpha receptor agonist molecule is essential in the management of the allergic reaction. Trying to suppress the complaints by adding topical corticosteroid drops to the existing therapy is a wrong approach, which cannot solve the problem but can easily create others (e.g. steroid induced ocular hypertension and steroid glaucoma). It is also essential to inform the patients that no other molecule from the same drug class can be used by them in the future, since cross allergy within the alpha agonist drug class and within different products containing the same active alpha receptor agonist ingredient is typical.

Passive venous dilation in the conjunctiva

In the last three decades topical prostaglandin analogue (PGA) eye drops became the first line glaucoma medications for OAG in most parts of the World. Topical PGAs provide a large IOP lowering effect and offer a convenient once a day instillation regimen. Ocular

hyperaemia related to topical PGA therapy is very common, typically minimal or mild, and is not associated with pain, eye opening difficulty or tearing [2,5]. Some degree of ocular hyperaemia in topical PGA users is almost unavoidable since PGA dilates veins (conjunctival veins). It is important for all ophthalmologists to understand that in contrast to the earlier described toxic and allergic hyperaemia forms, the PGA related ocular hyperaemia is a venous (non-inflammatory) redness, and usually requires no action form the treating ophthalmologists. The higher the concentration of the active PGA in the eye solution, and the higher the concentration of the preservative (BAK), the larger the hyperaemia. Thus, using modern formulations (a PGA with high receptor affinity and in low concentration, and a preservative-free solution) result in better patient satisfaction [6]. Glaucoma patients need to be informed on the possible mild conjunctival hyperaemia before the first PGA medication is initiated, in order to prevent unnecessary anxiety and early cessation of an effective IOP lowering therapy.

Passive episcleral vein dilation in topical Rho kinase inhibitor eye drop users

The Rho kinase inhibitors (ROCK inhibitors) represent the newest drug class of the IOP lowering medications [2]. Recently, these molecules became commonly used to reduce elevated IOP in OAG. They relax the trabecular meshwork and therefore increase the conventional aqueous humour outflow. But they also relax the episcleral veins and reduce the episcleral venous pressure, which plays an additional role in the increase of distal aqueous humour outflow. The relaxation of the episcleral veins leads to an increase of the diameter of the veins, which makes these vessels more visible (ocular hyperaemia). Thus, ocular hyperaemia due to topical ROCK inhibitor medication is a part of the mechanism of action. It is not associated with eye pain or eye-opening difficulties, but can cause anxiety if the patients are not informed before treatment initiation. The level of ocular hyperaemia is usually low in ROCK inhibitor users, but considerable individual differences exist.

Netarsudil, an IOP lowering ROCK inhibitor molecule is commonly manufactured in a fixed dose combination eye drop formulation, in which netarsudil and latanoprost (a PGA) are combined [7]. This is a very effective IOP lowering combination for a once a day instillation regimen, therefore it is more widely used than netarsudil in monotherapy. It is important to note that when this fixed dose combination drop is applied, ocular hyperaemia related to both the PGA component and the ROCK inhibitor component may appear [2]. Interestingly, in many cases the resulting hyperaemia remains low. Since neither the ROCK inhibitor related nor the PGA related ocular hyperaemia is inflammatory, no treatment cessation is indicated unless the cosmetic effect is disturbing for the patient.

Conclusion

Understanding ocular hyperaemia remains important for both glaucoma specialists and general ophthalmologists, and gains increasing clinical significance since new IOP lowering molecules are being developed for reducing IOP in glaucoma. Separating inflammatory/toxic hyperaemia (arterial dilation) and non-inflammatory hyperaemia (venous dilation) is essential, since the former form requires intervention (cessation of therapy, medication change, prevention of using other members of the allergenic drug class) while the latter form requires no action beyond patient information, unless the redness is cosmetically disturbing for the patient.

Acknowledgements and Conflicts of Interest

This editorial synthesizes publicly available evidence from international guidelines, systematic reviews and position papers. No conflicts of interest are declared by the author.

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