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Optimizing the care of the red eye patient: a new treatment direction

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HIGHLIGHTS

Brimonidine, a selective α_2-adrenergic agonist, reduces eye redness by acting on venous vessels without causing the symptoms of tissue hypoxia, acts quickly without causing the symptom of tachyphylaxis, and allows patients with red eye symptoms to improve the local condition and their quality of life.

ABSTRACT

Eye redness may be the result or symptom of various eye diseases or may appear for no apparent reason. In the case of red eye, therapeutic treatment is based on the correct diagnosis and, if possible, on causal treatment.

Therapeutic strategies in the treatment of local conjunctival hyperemia are also based on preventing vasodilation and thus reducing the red eye symptom.

Vasodilation is dependent on α-adrenergic receptors. Two classes of adrenergic receptors in the eye: α_1- and α_2-adrenergic receptors, which are responsible for the vascular tone of the conjunctiva. The end result of binding of agonists to α_1- and α_2-adrenergic receptors is vasoconstriction. However, the use of vasoconstrictor drugs is associated with the occurrence of tachyphylaxis, i.e. a decrease in effectiveness with long-term use and a rebound effect defined as hyperemia, which becomes even more severe after discontinuation of treatment. The introduction of brimonidine, which is a selective α_2-adrenergic agonist, into the treatment resulted in a reduction of these effects, which is also due to its effect on venous vessels and not causing the symptoms of tissue hypoxia. Compared to other vasoconstrictor drugs, it offers hope for patients with red eye symptoms to improve the local condition and their quality of life.

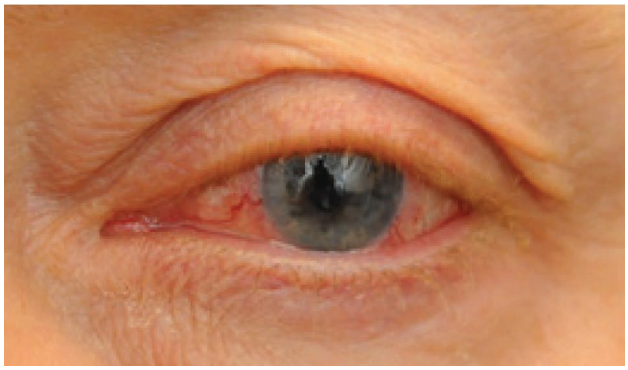
Key words: red eye, vasodilation, alpha-adrenergic receptors, selective alpha2-adrenergic agonist, tachyphylaxis symptom, rebound effect, brimonidine tartrate

RED EYE

Red eye is a common condition in the general population, and its diagnosis and treatment are the subject of ongoing debate. Patients often use the term "eye congestion" to describe this condition. Red eye can be the result of various eye diseases or it can manifest itself for no apparent reason. It can also change throughout the day, which can cause anxiety for patients.

FIGURE 1

Red eye – conjunctival redness.



The etiology of conjunctival hyperemia (fig. 1) can be divided into two distinct groups: severe and mild. When examining a patient, we should first rule out serious causes such as uveitis, closed-angle glaucoma, allergy or conjunctivitis. In addition, we should consider several less significant contributing factors, including exposure to irritating physical or chemical factors such as wind, low temperatures, smoke, air pollution, chlorinated water, cosmetics, exposure to tobacco smoke, light, computer screens, fatigue, and others. In addition, some patients may experience red eye after prolonged visual effort, such as office work, driving, or using electronic devices, called computer vision syndrome (CVS). Because of the potential for infectious complications that also cause red eye, contact lens wearers should be treated separately.

While the majority of red-eye cases are attributed to allergies or dry eye syndrome, many people associate it with going to bed late, alcohol or drug abuse, and being in rooms with tobacco smoke or irritating chemicals, such as those found in a swimming pool (chlorinated water). A separate group of patients must be considered, i.e. those who suffer from allergies. In such cases, red eye is most often an indication of contact with an allergen [1–4].

Some diagnostic tests for ocular disease cause red eye, which can be distressing to the patient. Surgical (e.g. LASIK) and diagnostic procedures that may cause isolated conjunctival hyperemia include applanation tonometry, Goldmann 3-mirror gonioscopy, ocular and orbital ultrasound, ultrasound biomicroscopy (UBM), or contact and immersion acoustic biometry [5, 6].

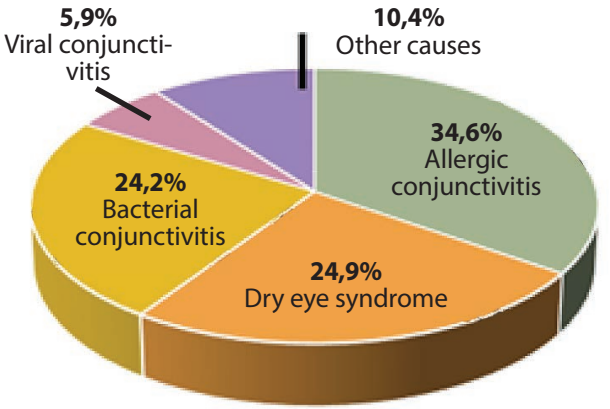
Conjunctival hyperemia is a pathophysiological condition involving vasodilation of the local conjunctival vasculature. It is characterized by prominent visible conjunctival vessels and conjunctival redness. Importantly, the anatomic structure of the vascular bed varies from patient to patient and may fluctuate throughout the day.

In such cases, patients often express concern about the appearance of their eyes, both because of the effects of the disease and the resulting cosmetic impact. However, patients often do not seek the advice of an ophthalmologist and instead use over-the-counter medications that do not always provide the desired results. In some cases, these medications can potentially worsen symptoms.

According to the literature, the frequency of visits for red eye is estimated at 15% of ophthalmology patients and approximately 6% of primary care patients [1, 2, 4]. Figure 2 shows the main reasons for these consultations, with emphasis on conjunctivitis and dry eye conditions.

FIGURE 2

Reasons for red eye consultation.



DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF RED EYE

Therapeutic management of red eye is based on proper diagnosis and, if possible, causal treatment.

In the case of infectious disease, appropriate antimicrobial management must be implemented. In the case of non-infectious red eye, treatment may be anti-allergic, focused on anti-inflammatory activity or intensive ocular surface hydration.

Therapeutic strategies to prevent vasodilation and reduce red eye are based on the treatment of local conjunctival hyperemia. For this purpose, patients often use over-the-counter products without differentiating between dilated arterioles and venules.

To determine how to prevent vasodilation, we need to understand the role of α-adrenergic receptors in regulating conjunctival vascular tone. The presence of α_1- and α_2-adrenergic receptors has been demonstrated in the eye. In both cases, the binding of an agonist to these receptors results in vasoconstriction [7–9].

EVOLUTION OF TOPICAL VASOCONSTRICTORS

The first α-adrenergic nonselective drug, epinephrine, was introduced in 1930. Development of the first α_1-selective drugs, phenylephrine and tetryzoline, began in 1931 and continued until 1950. This was followed by the introduction of mixed α_1- and α_2-adrenergic agonists, oxymetazoline and naphazoline, in 1970 and 1971, respectively. Significant progress was made in 2017 with the introduction of brimonidine tartrate (brimonidine), a selective α_2-adrenergic agonist [8].

As mentioned above, α_1- and α_2-adrenergic receptors mediate vasoconstriction. The use of vasoconstrictors is associated with tachyphylaxis, which is a progressive decrease in response to a given dose after repeated administration of a drug, and rebound, which is defined as the worsening of symptoms after discontinuation of treatment.

Drugs that reduce red eye, such as tetryzoline or nafazoline, cause shrinkage of conjunctival arterioles and venules, increasing the risk of rebound and tachyphylaxis.

The rebound effect is a result of constriction of arterioles caused by α_1- or mixed α_2/α_1-agonists. This constriction may reduce oxygen availability to the surrounding tissue, leading to ischemia and associated hypoxia. Prolonged periods of sustained hypoxia/ischemia may trigger the release of compensatory vasodilators, contributing to the rebound effect [9, 10].

This phenomenon can be mitigated by the use of α_2-agonists, which induce vasoconstriction, thereby preventing oxygen deprivation in the conjunctiva and averting the rebound effect.

Interestingly, despite the side effects, tachyphylaxis and rebound associated with older-generation drugs, the number of OTC packages of tetryzoline drops sold in a 12-month period reached 1,295,979 units (April 2024), 1,115,638 units (May 2024). Source: IQVIA, Pharmascope MAT/05/2024.

NEW DRUG, DIFFERENT MECHANISM OF ACTION

Brimonidine (brimonidine tartrate) is a highly selective third-generation α_2-adrenergic receptor agonist, which is an imidazoline derivative. In this case, selectivity means that the drug has a much stronger affinity for the α_2-receptor than for the α_1-receptor, approximately 1000:1. In 1996, Burke showed that it is 7–12 times more selective for α_2-adrenergic receptors than clonidine and 28–32 times more selective than apraclonidine.

The drug acts by constricting venous blood vessels, which reduces the risk of ischemia and hypoxia, causes contraction of primarily conjunctival venous vessels, produces minimal or no rebound effect, and is less likely to cause tachyphylaxis [4, 11, 12].

Brimonidine tartrate is available in a variety of forms, concentrations and indications. In dermatology, it is used as a prescription dermatologic gel at a concentration of 0.33% for the treatment of persistent (non-transient) facial erythema associated with rosacea. Also topically as a prescription ophthalmic drug at concentrations >0.1% to lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). It acts on α_2-adrenergic receptors in the iris and ciliary body to lower IOP by reducing aqueous humor production. It also increases outflow through the choroidal-retinal pathway in the long term. This mechanism of action provides advantages over traditional α_1-agonist-containing or mixed medications [13, 14].

The potent vasoconstrictor effect of brimonidine at low concentrations led to the development of a new concentration of brimonidine tartrate and clinical trials that confirmed the drug's efficacy and safety. It has recently been approved by the US Food and Drug Administration (FDA) [6, 14].

CLINICAL TRIALS

McLaurin et al. designed a double-blind clinical trial to evaluate the change in redness at 1, 360 and 480 min compared to the pre-treatment condition and the control group. The degree of redness after 7 days was also determined. The analysis confirmed the efficacy and safety of brimonidine [15].

Torkildsen et al. described the effects of brimonidine in 42 selected patients. Changes in erythema were assessed by the investigator and the patient during 28 days of treatment. Efficacy, rebound effect, and incidence of adverse events were determined. It was found that investigator-rated eye redness was significantly less after brimonidine administration throughout the observation period. No tachyphylaxis was observed. There were no serious adverse events, only transient symptoms of mild discomfort. This suggests that a new-generation vasoconstrictor such as brimonidine has a more favorable effect at low concentrations than older-generation drugs, which are often associated with tachyphylaxis and rebound effects. This has been confirmed in other clinical studies [16].

Thus, clinical studies have demonstrated the efficacy and safety of brimonidine tartrate (0.025%), confirming that its use is not associated with tachyphylaxis, that the rebound

effect is minimal or absent, and that there are no serious side effects [15-17].

The recommended dosage of 0.25 mg brimonidine tartrate (0.025%) as Lumobry®: 1 drop in each affected eye every 6–8 h (maximum 4 times a day). Redness should subside within 5–15 min. If the condition worsens or symptoms do not resolve within 3 days, consult an ophthalmologist.

The pictures show the reduction of the patient's congestion 15 min after the application of the drug (fig. 3, 4).

FIGURE 3

Conjunctival, scleral, and corneal congestion in a patient with a blind eye and post-inflammatory scar before drug application.

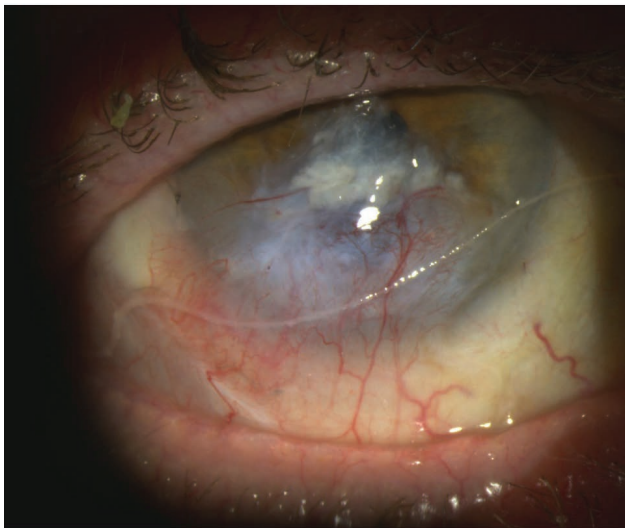
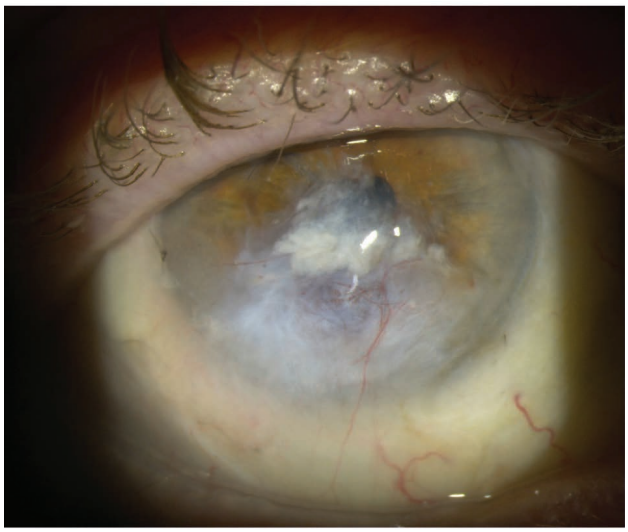


FIGURE 4

The patient in figure 3, 15 min after drug application. Significant bleaching of the eye can be observed, with shrinkage of the vessels growing into the cornea.



CONCLUSIONS

Red eye, also known as conjunctivitis, is a condition that requires a detailed diagnosis to determine the underlying cause and implement the appropriate treatment. If the cause of the redness is identified, a targeted therapy can be prescribed. However, if the redness occurs without a clear pathology, vasoconstrictive medications may be used as a treatment.

Vasoconstrictive medications should be used responsibly, with a maximum duration of a few days, bearing in mind that in certain cases, such as dry eye disease, they may aggravate the symptoms. However, they may be effective in allergic conjunctivitis, which is characterized by redness of the eye due to exposure to irritating physical or chemical factors such as wind, low temperature, smoke, air pollution, chlorinated water, or cosmetics. In addition, their use may be beneficial after prolonged visual effort, whether from office work, driving, or using electronic devices. The mechanism of action of vasoconstrictive drugs involves interaction with α_1- and α_2-adrenergic receptors.

Drugs that reduce red eye symptoms with tetryzoline or nafazoline cause contraction of both arterioles and venules in the conjunctiva, so there is a risk of a rebound effect, tachyphylaxis, or decreased efficacy.

Brimonidine tartrate, a selective α_2-adrenergic receptor agonist and imidazoline derivative, has been shown to have minimal side effects and, unlike other drugs, is not associated with tachyphylaxis or rebound. It is the latest drug to offer patients with red eye symptoms hope for improvement in their local condition and quality of life.

Figures: from the author's own materials.

TABLE 1

Development work program for Lumobry®: brimonidine tartrate ophthalmic solution (BTOS) 0.025%.

Phase	Study number	Study title
2/3	11-100-0015 NCT01675609	Safety and efficacy of BTOS 0.025% in adults and the elderly
3	13-100-0005 Study 861 NCT01959230	Safetyand efficacy of BTOS 0.025% in adults and elderly with eye redness
3	13-100-0006 Study 862 NCT01959243	Safety of BTOS 0.025% in children, adolescents, adults and the elderly
1	13-100-0007 Study 863 NCT02039765	Pharmacokinetics and safety of topical administration of BTOS 0.025%
2	10-100-0008 NCT01275105	Evaluation of dose-dependent duration of action of BTOS 0.01% and BTOS 0.025% for control of CAC-induced eye redness
1 (pilot study)	12-150-0001 NCT01687426	Safety of BTOS 0.025% and IOP-lowering response in subjects with OAG or OHT

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The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.