

REVIEW ARTICLE

40 years of topical beta-blockers for glaucoma

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**Abstract**

The introduction of topical beta-blockers in 1978 was a major breakthrough in the treatment of ocular hypertension and glaucoma, and although no longer first-line, beta-blockers remain a commonly prescribed and important intraocular pressure (IOP) lowering medication. On the 40th anniversary of their introduction we critique the current role of topical beta-blockers, with particular regard to their efficacy, side effects, and role in fixed-dose combinations. While beta-blockers are effective at lowering IOP during the day, sleep laboratory studies have shown that they have minimal effect overnight, likely due to the physiological nocturnal reduction in aqueous production. Cardiac and respiratory side effects are especially important to consider in elderly patients with multiple comorbidities or in those using multiple systemic medications, which may affect beta-blocker metabolism. The increasing number of alternative medical and minimally invasive surgical options for glaucoma treatment is likely to see a reduction in beta-blocker prescribing.

Introduction

This year marks the 40th anniversary of the introduction of topical beta-blockers for the treatment of glaucoma. Before 1978, the medical treatment of glaucoma relied on the non-selective adrenergic agonist, epinephrine, and the cholinergic agonist, pilocarpine; consequently, the availability of topical timolol maleate represented a major breakthrough in intraocular pressure (IOP) lowering therapy. Timolol became the first-line medical treatment for glaucoma and ocular hypertension (OHT) and remained the undisputed initial choice until the introduction of prostaglandin analogs in 1996.

Although, for most patients, prostaglandin analogs are now the first-line medical treatment, topical beta-blockers remain a widely prescribed and valuable medication, particularly as constituents of fixed-dose combination treatments. However, many patients have contraindications to beta-blockers, which can be associated with potentially serious systemic side effects, and there are concerns regarding their potentially adverse effect on ocular blood flow and lack of 24-h efficacy. On the 40th anniversary of the introduction of topical timolol and given

the wide range of alternative medical, laser, and minimally invasive surgical options, it seems appropriate to consider the role of topical beta-blockers in glaucoma treatment today.

Pharmacology

Beta-blockers act on the post-synaptic β_1 - and β_2 -adrenergic receptors of the sympathetic division of the autonomic nervous system.^[1] Blockade of β_1 -receptors in the ciliary body leads to reduced aqueous humour production; however, β_1 -blockade also leads to reduced heart rate, reduced cardiac output, and lower blood pressure.^[2,3] Blockade of β_2 receptors results in bronchoconstriction and vasoconstriction, leading to potential side effects including dyspnea, worsening of Raynaud's syndrome, and erectile dysfunction. β_2 -blockade also affects the liver and pancreas, with consequent decreased gluconeogenesis and lipolysis and reduced insulin secretion.^[4] When a patient instills an eye drop, only 2–10% reaches the site of action at the ciliary body. The remainder enters the systemic circulation through conjunctival vessels, nasal mucosa through the nasolacrimal duct, and upper gastrointestinal tract. Therefore,

similar to intravenous administration, drugs given topically bypass first-pass metabolism and can reach relative high plasma concentrations. Topical timolol achieves peak plasma concentration within 5–30 min and has a half-life of 4 h, with one drop of 0.5% timolol equivalent to a 10 mg oral dose. Although systemic absorption can be reduced with nasolacrimal duct occlusion, the amount of drug entering the systemic circulation remains high.

Timolol is eliminated from the body largely through metabolism by CYP2D6, a cytochrome P450 enzyme. It is estimated that 6–10% of Caucasians, 2–5% of African-Americans and 1% of Asians have an inherited deficiency of CYP2D6, which may lead to increased susceptibility to timolol-related side effects. At least one study has shown poor metabolizers have higher plasma concentrations of timolol and more pronounced bradycardia after administration of timolol eye drops.^[5] Older age, hepatic impairment, and medications, including tricyclic antidepressants, codeine, and tramadol, which are also metabolized by CYP2D6, may also increase the risk of systemic side effects with ophthalmic β -blockers.^[6,7] Although the selective β 1-blocker betaxolol has a lower risk of causing respiratory side effects, it has a similar effect on cardiac function and blood pressure, with the magnitude of systemic side effects similarly affected by variation in metabolism.^[6]

Efficacy

Numerous prospective randomized trials have proven that lowering IOP reduces the risk of glaucomatous visual loss, with the recent United Kingdom Glaucoma Treatment Study, the first study showing the effectiveness of medical treatment (latanoprost) compared to placebo.^[8,9] Studies establishing the value of topical beta-blockers in OHT and glaucoma include the landmark Ocular Hypertension Treatment Study^[8] and Early Manifest Glaucoma Treatment Trial,^[9] which were initiated before prostaglandin analogs became available. Although beta-blockers are effective IOP lowering medications, they are less effective than prostaglandin analogs. Pooled results from studies including over 800 patients found an average 26% reduction in IOP with timolol 0.5% twice per day, compared to a 31% reduction with latanoprost, with the advantage that latanoprost requires once-daily administration and has fewer systemic side effects.^[5,10]

An additional concern regarding beta-blockers, which is now well established from studies in the sleep laboratory, is that they lack 24-h efficacy, with their effect diminished during the nocturnal period.^[11] A recent prospective, randomized, double-masked crossover study found that, while both prostaglandin analogs and beta-blockers reduced mean 24-h IOP, prostaglandin analogs were more effective than beta-blockers during the night, and patients using beta-blockers had reduced blood pressure, heart rate, and ocular perfusion pressure, which may have important consequences for glaucoma progression.^[11] Furthermore, when used as a second line agent in patients

already using a prostaglandin analogue, although timolol 0.5% twice per day further lowered IOP during the day, it had no effect on nocturnal IOP. The likely explanation for the lack of nocturnal efficacy is that beta-blockers' mechanism of action relies on impeding the effects of endogenous catecholamines, which drive aqueous humor formation in the ciliary epithelia. In normal individuals, aqueous production decreases to half of the daytime levels during sleep, reducing the opportunity for beta-blockers to further reduce aqueous production.^[12]

Due to lower efficacy and higher risk of systemic side effects compared to prostaglandin analogs, topical beta-blockers are no longer the first-choice treatment for most patients with glaucoma or OHT. Yet, patients frequently require more than one medication and beta-blockers are the foremost second-line treatment, particularly given their availability in fixed-dose combination formulations. Furthermore, although beta-blockers are no longer first line for all, the most appropriate first choice medication will differ according to the individual ocular and systemic comorbidities and beta-blockers or an alternative may be preferable to prostaglandin analogs in patients with comorbidities such as herpetic eye disease or cystoid macular edema. It is, therefore, crucial to tailor treatment according to patients' individual needs.^[13]

Adherence to treatment is also essential to treatment success, and previous studies have shown decreasing adherence with increasing numbers of medications.^[14,15] An advantage of topical beta-blockers is that they are available in fixed combination formulations which are likely to improve adherence in those needing more than one agent. A recent study examining adherence to glaucoma medications found that, over a 1-year period, patients using two separate IOP-lowering medications instilled their drops within 24 h of expected on only $43 \pm 27\%$ of days compared to $60 \pm 28\%$ of days for those using fixed combination medications. No patients using separate drops were adherent for >95% of days.^[16] Due to the effect of complex dosing regimens on adherence and the greater exposure to preservatives with a greater number of drops, it is recommended to use fixed-dose combination medications when available.^[17] A disadvantage of beta-blocker containing fixed-dose combinations, however, is that they contain timolol at a concentration of 0.5%, which may expose the patient to greater risk of systemic side effects, with no greater IOP-lowering efficacy compared to lower concentrations such as 0.25% and 0.1%. Furthermore, in countries where prostaglandin analog - beta-blocker fixed combination medications are available, there is controversy regarding the optimal timing of administration. While prostaglandin analogs are typically taken in the evening, due to the lack of nocturnal IOP lowering and the potential for reduced blood pressure and ocular perfusion pressure, there is a preference among many ophthalmologists for beta-blockers to be administered in the morning. Furthermore, prostaglandin analog - beta-blocker fixed combination medications are not currently available in the United States as the U.S. Food and Drug Administration has stipulated, new combinations must demonstrate a 2 mmHg further reduction in IOP than provided

by either individual component. When beta-blockers are used as a second-line agent, a meta-analysis examining the additive effect of alpha-agonists, beta-blockers, and carbonic anhydrase inhibitors combined with prostaglandin analogs showed a similar mean additional IOP-lowering effect of approximately 2.3–3 mmHg for each medication.^[18] However, no individual studies of prostaglandin analog - beta-blocker fixed combination medications - have met the FDA criteria for approval.

Side effects and Contraindications

Topical administration of beta-blockers may cause systemic side effects as β -adrenergic receptors are expressed by cardiac muscles, airways, arteries, and kidneys and in the sympathetic nervous system. However, due to strict inclusion criteria, the systemic side effects of topical beta-blockers may be underestimated in pivotal Phase 3 trials compared to real-world experiences. The medication package insert for timolol, in which patients often read when first prescribed the medication, lists systemic side effects including low blood glucose levels, insomnia, depression, anxiety, nightmares, memory loss, slow heart rate, palpitations, heart failure, heart block, low blood pressure, Raynaud's phenomenon, cold hand and feet, constriction of the airways of the lungs, nasal congestion, cough, loss of appetite, nausea, dry mouth, indigestion, fainting, muscle weakness, stroke, reduced blood supply to the brain, worsening myasthenia gravis, hair loss, worsening of psoriasis, muscle pain, and sexual dysfunction. Although many of these potential side effects are rare, it is important to be aware of the potential for harm when prescribing.

The use of topical beta-blockers is contraindicated in patients with asthma or chronic obstructive pulmonary disease (COPD), hypotension, bradycardia, or Raynaud's disease, and they should be used in caution in diabetes due to the risk of masking signs and symptoms of hypoglycemia. They are also relatively contraindicated in patients using systemic beta-blockers and, as previously discussed should, be used in caution in patients using other CYP2D6 inhibitors such as paroxetine and fluoxetine. Due to the large number of contraindications, it is essential for prescribers to take a comprehensive past medical history and medication history before initiating any glaucoma treatment. Glaucoma patients are often elderly with multiple comorbidities and hence are on multiple systemic medications. It is also important to be aware that some patients may have undiagnosed comorbidity and it is, therefore, prudent to check the patient's pulse rate and blood pressure before prescribing a beta-blocker and to provide a warning of potential side effects of treatment, so medication can be discontinued promptly if side effects occur.

Cardiac Safety

The effect of topical timolol on heart rate and blood pressure is well established.^[19] For example, a double-masked crossover study including 43 subjects with glaucoma evaluated the effect

of timolol 0.5% eye drops twice per day on 24-h heart rate compared to placebo.^[20] There was a significant decrease in heart rate, with an average decline of 6 beats per minute, although the decline was more pronounced if patients were coprescribed an oral beta-blocker. As previously noted, bradycardia was also more marked in those with impaired CYP2D6 function.^[5,21] The effects of bradycardia may go unnoticed by the patient; however, bradycardia it may lead to tiredness on exertion, breathlessness, and combined with hypotension; lower ocular and brain perfusion and increased risk of falls. A study from Australia, including over 6000 patients, found that recent commencement with timolol eye drops was a significant risk factor for hospitalization due to bradycardia.^[22]

Another recognized side effect is orthostatic hypotension, defined as a decrease in systolic BP of >20 mm Hg or diastolic >10 mm Hg within 3 min of standing or head up tilt.^[23] Orthostatic hypotension can lead to falls, which are a serious problem in the elderly. 30% of people above the age of 65 years old fall at least once per year,^[24] with falls associated with increased morbidity and mortality, as well as reduced quality of life, in part due to patients limiting normal daily activities. It is important to consider the risk of falls when prescribing elderly patients with topical beta-blockers. A retrospective study of 500 patients with glaucoma aged 65 years or more found that 10% of patients using timolol had experienced an injurious fall in the previous year compared to only 3% of patients not using antiglaucoma medications.^[25] Although it did not control for different levels of activity, a recent prospective study including 2400 patients followed for 2–3 years found that the risk of falls in those using topical timolol was very similar to those using oral beta-blockers, with patients using either topical or systemic beta-blockers at higher risk of falls than those not treated with beta-blockers.^[26] Topical timolol was associated with a 1.37-fold (95% confidence interval [CI] 0.99–1.90) increased risk of falls, whereas non-selective systemic beta-blockers were associated with 1.4-fold (95% CI 1.12–1.78) increased risk. To reduce the risk of orthostatic problems, the authors recommended using a lower concentration of 0.1% timolol.^[26,27]

A rarer side effect is the impact of beta-blockers on cardiac conduction, and there are several reports of previously healthy patients developing complete heart block following treatment with topical timolol, with some patients requiring implantation of permanent pacemakers.^[19]

Pulmonary Safety

Topical beta-blockers may also exacerbate asthma and COPD and are contraindicated in these patients. A retrospective analysis of prescribing habits, examined using a UK electronic patient record, identified almost 5000 asthmatics who were newly prescribed topical IOP lowering medication between 2000 and 2012.^[28] Approximately 1 in 5 was given a non-selective beta-blocker, disagreeing with known contraindications, which was similar to previous reports of high frequency of beta-blocker prescription in asthmatics.^[29] This suggests that

prescribers are not enquiring about patients' comorbidities. Of the 1369 patients prescribed a topical beta-blocker, 128 had a severe asthma exacerbation requiring hospital admission during follow-up, while another 298 had moderate exacerbations requiring treatment with oral steroids. The risk of asthma exacerbation was highest within 30 days of starting topical beta-blockers (IRR = 4.83, 95% CI 1.56–14.9); however, there was no significant increase in exacerbations with chronic use, perhaps as patients at risk of exacerbation had already discontinued topical beta-blockers. Interestingly, the risk of asthma exacerbation was similar between selective and non-selective beta-blockers, similar to the results of Kirwan *et al.* study discussed below.^[30]

The general decline in beta-blocker prescribing seems to have resulted in a reduction in the number of asthmatic patients prescribed beta-blockers. In the UK study, non-selective and selective topical beta-blocker prescribing decreased from 23% to 13.4% and 10.5% to 0.9% respectively between 2000 and 2012, however the level of topical beta-blocker prescribing in patients with asthma remains high with >1 in 10 patients with asthma and OHT or glaucoma prescribed a topical beta-blocker.^[31] The reason for the fall in betaxolol prescribing, despite its better safety profile, was perhaps due to the increased availability of fixed combination preparations containing non-selective beta-blockers. In addition to an increased risk of exacerbation of known obstructive pulmonary disease, there is a evidence of previously undiagnosed patients developing symptoms of obstructive airway disease after commencing topical beta-blockers. Specifically, Kirwan *et al.* reported an increase in new prescriptions for obstructive airways disease after starting topical beta-blockers with a hazard ratio of 2.22 (95% CI 1.63 to 3.02) for non-selective topical beta-blockers compared to controls and a similarly high hazard ratio of 3.06 (95% CI 1.63–5.36) for selective topical beta-blockers, suggesting that selective beta-blockers may not be as safe for asthmatics as initial thought.^[30]

Studies examining the respiratory effects of topical beta-blockers in terms of respiratory function have also shown an adverse effect. Acute non-selective beta-blocker eye drop exposure has been shown to result in a significant mean fall in forced expiratory volume 1, with an average fall of almost 11%, and a decrease in pulmonary function similar to the effect of exposure to oral beta-blockers.^[28] A recent population-based study of almost 100,000 patients newly prescribed IOP lowering treatment found that patients using medication for pulmonary disease had a significantly higher chance of stopping beta-blockers within 90 days of commencement compared to those without pulmonary disease (8% vs. 4%).^[32] The rate of discontinuation of other IOP lowering medications was similar regardless of whether the patient had asthma or COPD.

Other Side Effects

Other side effects reported with topical beta-blockers include effects on the central nervous system such as depression,

hallucinations, or confusion, which may be misattributed to dementia in elderly patients. Just as it is important for ophthalmologists to be aware of a patient's systemic medication, it is important that family doctors and physicians are aware of the patient's ophthalmic medications and their potential side effects so that symptoms, due to medication side effects, are not attributed to old age or systemic disease.

Polypharmacy

Elderly patients commonly use multiple medications, with many using either systemic beta-blockers or CYP2D6 inhibitors, which can increase the likelihood systemic side effects and, for systemic beta-blockers, reduce the efficacy of topical beta-blockers. A recent study which evaluated ophthalmic drugs as part of polypharmacy in nursing home residents with glaucoma found that patients were prescribed an average of six systemic medications, with 20% using both a systemic and topical beta-blockers.^[33] An Australian study also found a 20% rate of coprescribing of topical and systemic beta-blockers.^[34] Several studies have shown that concurrent use of a systemic β -blocker reduces the efficacy of a topical β -blocker while increasing the risk of systemic side effects.^[20,21,34,35] For this reason, we recommend avoiding concurrent use of topical and systemic beta-blockers.

Of concern, the Blue Mountains Eye Study suggested a possible increase in cardiovascular mortality for patients previously diagnosed with glaucoma, particularly noted among those using timolol. However, the reason for possible increased mortality was not certain and the results have not been corroborated.^[36] A further important study to consider is the low-pressure glaucoma treatment study,^[37] which is often interpreted as demonstrating a harmful effect of topical timolol 0.5% in patients with normal tension glaucoma (NTG). The study, which included 178 patients with NTG randomized to timolol or brimonidine, found that although there was no significant reduction in IOP between groups, patients using timolol had a significantly higher risk of progression, with 39.2% of the timolol group noted to have visual field progression compared to only 9.1% of the brimonidine group over an average 30-month follow-up period. This suggests that either brimonidine had a neuroprotective effect beyond IOP lowering or that timolol was harmful, perhaps, due to reduced ocular perfusion during the night. However, the study was affected by a large dropout rate, particularly in the brimonidine arm, which limits our ability to draw definitive conclusions.

In summary, 40 years since their introduction, although no longer the first-line treatment for most patients, beta-blockers remain a commonly prescribed and important IOP lowering medication. However, while beta-blockers are effective at lowering IOP during the day, sleep-laboratory studies have shown that they have minimal effect overnight, likely due to the physiological nocturnal reduction in aqueous production. Lack of nocturnal IOP lowering, coupled with the propensity to lower blood pressure, means that topical beta-blockers may reduce

ocular perfusion pressure at night, with the potential to have a detrimental effect on glaucoma progression. Before prescribing beta-blockers, it is essential to take a thorough past medical and medication history, and if beta-blockers are considered, we would recommend checking blood pressure and pulse rate before starting treatment. A recent review article went as far as to recommend patients should have their CYP2D6 genotype assessed prior to commencing treatment with topical beta-blockers;^[19] however, this is unlikely to be practical in clinical practice and advising patients to be aware of possible side effects and monitoring pulse rate and blood pressure may be more realistic. The use of topical beta-blockers, while not absolutely contraindicated, should also be reconsidered if patients are the elderly, have multiple comorbidities, or are using multiple systemic medications, particularly systemic beta-blockers. There is also a strong argument for the use of weaker beta-blockers, such as timolol 0.1%, which have similar efficacy but less potential for systemic side effects. Fixed combination medications are important to consider given the evidence of higher adherence rates than with separate medications; however, more evidence is needed regarding the optimal timing of fixed-dose prostaglandin analog - beta-blocker combinations, and there is a need for fixed-dose combinations containing weaker concentrations of timolol. Therefore, while we have four decades of experience using topical beta-blockers for glaucoma, there are still questions unanswered regarding their optimal use. Given the emergence of less invasive glaucoma surgical procedures, there are, however, likely to be fewer patients needing multiple eye drops for glaucoma. With the increasing number of therapeutic options available, it becomes increasingly important to tailor treatment choices to the individual needs of each patient.

Disclosure

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