

Preservative free 2% carteolol and other topical β -blockers in glaucoma therapy: indications, contraindications and safety profile



Jaromir Wasyluk^{1,2}

¹ Department of Ophthalmology, Military Institute of Aviation Medicine, Warsaw
Head: Radosław Różycki, Md, PhD

² OPTIMUM Eye Center, Warsaw
Scientific director: Jaromir Wasyluk, MD, PhD

HIGHLIGHTS

Preservative free 2% carteolol comparing to other β -blockers may be a valuable alternative in glaucoma first choice therapy thanks to some pharmacological properties, distinguishing this drug among others in this group.

ABSTRACT

Topical β -blockers, both selective and non-selective, are first-line therapeutic options in different types of glaucoma, particularly in its most common type – open angle glaucoma. In this paper the author is summarizing and comparing characteristics of β -blocker ophthalmic drops accessible in Poland: carteolol, betaxolol and timolol, describing indications and contraindications for their use in glaucoma therapy, possible adverse effects and general safety profile. Preservative free 2% carteolol ophthalmic solution, compared to other topical β -blockers, indicates that it may be a valuable alternative in first choice glaucoma therapy, thanks to some properties, which distinguish the drug within the group. Its sufficient hypotensive effect enables 2% carteolol to be used in glaucoma monotherapy, the unique intrinsic sympathomimetic activity allows safer application in patients with some concomitant systemic diseases and once-daily long acting preservative free formula simplifies dosing, improves patient's adherence and persistence in and increases therapy comfort, minimizing adverse effects on ocular surface.

Key words: glaucoma therapy, topical β -blockers, intrinsic sympathomimetic activity, safety profile

INTRODUCTION

Glaucoma comprises a group of optic neuropathies characterized by progressive loss of retinal ganglion cells and their axons, leading to characteristic optic nerve head cupping and corresponding visual field defects. Glaucoma is the leading cause of irreversible vision loss worldwide and the second leading cause in developed countries. It is estimated to affect approximately 76–78 million people globally [1–3]. In Poland, approximately 800,000 people are affected [4], fewer than half of whom have been diagnosed and are receiving treatment.

Based on the underlying pathophysiology and the anatomy of the anterior chamber angle, glaucoma is classified as open-angle or angle-closure glaucoma. According to etiology, it is classified as congenital, primary, or secondary glaucoma.

Open-angle glaucoma (OAG) is a chronic, incurable disease; however, early diagnosis and appropriate treatment can significantly slow the progression of visual field loss, allowing patients to preserve useful vision and maintain a satisfactory quality of life. The only treatment for glaucoma whose efficacy has been demonstrated in multicenter randomized clinical trials is lowering intraocular pressure (IOP), regardless of the baseline IOP level [5]. This applies to all types and subtypes of glaucoma, including both high-pressure glaucoma and glaucoma in which IOP remains within the statistically normal range. The latter subtype of open-angle glaucoma is referred to as normal-tension glaucoma (NTG).

GLAUCOMA TREATMENT ALGORITHMS

This article focuses primarily on the management of open-angle glaucoma, including both high-pressure and normal-tension glaucoma, as these forms account for the majority of glaucoma cases in the population. Congenital glaucoma is treated predominantly with surgery, whereas angle-closure glaucoma generally requires laser or surgical intervention. In these forms of glaucoma, topical IOP-lowering therapy has only a limited adjunctive role.

As noted above, lowering intraocular pressure remains the cornerstone of glaucoma treatment. The European Glaucoma Society Guidelines (EGS Guidelines) [6], which are regularly updated to reflect current terminology, diagnostic standards, and therapeutic strategies, provide a clear treatment algorithm for patients with open-angle glaucoma. In the latest 2025 edition, prostaglandin analogues (PGAs) are recommended as first-line monotherapy because of their strong IOP-lowering effect, convenient once-daily dosing, and favorable safety profile. If additional treatment is required, topical β -blockers are generally considered the next pharmacological option. However, it is important to distinguish between “first-line therapies,” meaning treat-

ments recommended by national and international guidelines, and the “first-choice treatment,” meaning the therapy selected by the treating physician as the most appropriate initial option for an individual patient. Depending on the clinical context, the initial pharmacological treatment may therefore be chosen from several drug classes, including β -blockers, carbonic anhydrase inhibitors (CAIs), α_2 -adrenergic agonists, and prostaglandin analogues (PGAs). In selected patients with open-angle glaucoma, selective laser trabeculoplasty (SLT) may also be used as an alternative first-line treatment to topical medication.

GENERAL CHARACTERISTICS OF β -BLOCKERS

β -blockers have been used in medicine for many decades, primarily in the treatment of arterial hypertension, ischemic heart disease, heart failure, and selected cardiac arrhythmias, as well as as adjunctive therapy for migraine and hyperthyroidism. In ophthalmology, they are also among the longest-established topical agents. Timolol was introduced for the treatment of glaucoma in 1978, following pilocarpine, which had been introduced almost a century earlier, and carteolol was added to the β -blocker class in 1984.

In open-angle glaucoma, β -blockers lower intraocular pressure by selectively or nonselectively antagonizing β_1 - and β_2 -adrenergic receptors in the ciliary epithelium. Activation of these receptors promotes aqueous humor secretion, whereas their blockade reduces aqueous humor production. Ophthalmic β -blockers include timolol, carteolol, betaxolol, levobunolol, and metipranolol. Of these, timolol, carteolol, and betaxolol are currently available in Poland.

Carteolol and timolol are nonselective β -blockers that antagonize both β_1 - and β_2 -adrenergic receptors. This broader receptor blockade is associated with a greater IOP-lowering effect but also with a higher risk of systemic adverse effects. Betaxolol is a β_1 -selective, or cardioselective, β -blocker and may therefore be preferable in patients with glaucoma who also have bronchial asthma or chronic obstructive pulmonary disease (COPD). However, its IOP-lowering efficacy is significantly lower than that of the nonselective agents in this class.

The most clinically relevant systemic adverse effects associated with topical ophthalmic β -blockers include bradycardia, worsening of atrioventricular conduction disturbances, exacerbation of heart failure, deterioration of renal function, adverse effects on lipid metabolism and glycemic control, and worsening of bronchial asthma or chronic obstructive pulmonary disease (COPD). In many cases, systemic exposure can be reduced by instructing patients in proper eye-drop instillation technique. Measures such as nasolacrimal occlusion, keeping the eyes gently closed after

instillation, and avoiding blinking for several minutes can help limit systemic absorption.

Topical β -blockers are generally well tolerated. Local adverse effects may include worsening of dry eye symptoms, related to reduced corneal sensitivity and decreased tear secretion, as well as ocular irritation and conjunctival hyperemia. Conjunctival hypertrophy involving the palpebral and bulbar conjunctiva, potentially leading to obstruction of the lacrimal puncta, has also been reported, particularly with timolol. Some studies have suggested that timolol may reduce blood flow at the optic nerve head, possibly as a result of vasoconstriction, whereas betaxolol and carteolol have been associated with more favorable effects on ocular perfusion.

ROLE OF β -BLOCKERS IN GLAUCOMA THERAPY

As outlined above, β -blockers are most commonly used as second-line monotherapy or as an adjunct to other IOP-lowering agents, including prostaglandin analogues (PGAs), α_2 -adrenergic agonists, and carbonic anhydrase inhibitors (CAIs), either in fixed-combination preparations or as part of multidrug therapy. In selected clinical situations, however, β -blockers may also be considered as initial therapy for glaucoma. These include:

- ocular intolerance to topical prostaglandin analogues, with reported rates ranging from 10% to 36% across studies [7–9]
- an inadequate IOP-lowering response to prostaglandin analogues (“non-responders”), reported in approximately 15–30% of patients [10, 11]
- patient reluctance to use prostaglandin analogues because of potential periocular cosmetic adverse effects, including increased iris pigmentation, eyelid hyperpigmentation, and excessive eyelash growth)
- contraindications to prostaglandin analogue therapy, including inflammatory glaucoma; anterior or posterior uveitis [12]; a history of herpetic keratitis because of the risk of reactivation [13–15]; and aphakia or pseudophakia with posterior capsule rupture because of the risk of cystoid macular edema).

A substantial proportion of middle-aged and older patients receive systemic β -blockers for common cardiovascular conditions, including arterial hypertension and ischemic heart disease. In these patients, the use of an additional topical β -blocker requires consideration of both potential systemic effects and ocular efficacy. Although topical treatment may provide further IOP reduction in some patients, the hypotensive response may be attenuated in those already receiving systemic β -blocker therapy [16]. Accordingly, concomitant systemic treatment should be taken into account when selecting and monitoring topical β -blocker therapy. As noted above, lowering intraocular pressure is

the cornerstone of glaucoma management and remains the key modifiable factor for preserving visual function. Long-term treatment success, however, also depends on several additional factors, particularly adherence to therapy and persistence with the prescribed regimen. Both are strongly influenced by local and systemic tolerability, as well as by the complexity of the dosing schedule. Unlike treatments for many symptomatic conditions, topical glaucoma therapy does not improve vision or provide an immediate perceptible benefit, although patients may initially expect such an effect. Because treatment is typically lifelong, the therapeutic regimen should therefore be as simple, well tolerated, and minimally burdensome as possible, while avoiding clinically significant adverse effects.

SPECIFIC FEATURES OF PRESERVATIVE-FREE 2% CARTEOLOL

IOP-lowering efficacy and effects on ocular blood flow

Carteolol can reduce intraocular pressure by approximately 20–25%, an effect comparable to that of timolol [17, 18], although some studies suggest slightly lower efficacy. It may therefore be considered as initial monotherapy in selected patients with glaucoma [19].

Although IOP reduction remains the cornerstone of glaucoma treatment, ocular blood flow may also be relevant in normal-tension glaucoma, in which vascular dysregulation is frequently reported. Some studies have suggested that carteolol may have favorable effects on blood flow in the posterior segment of the eye in patients with glaucoma [20–22], whereas others have not demonstrated a consistent or significant effect [23, 24].

Carteolol may also be used as part of combination therapy with agents from other pharmacological classes, including prostaglandin analogues (PGAs), carbonic anhydrase inhibitors (CAIs), and α_2 -adrenergic agonists, providing an additive or synergistic IOP-lowering effect through complementary mechanisms of action [25]. Several studies have evaluated a fixed combination of carteolol and latanoprost, which is not currently available in Poland [26]. These studies reported a 24-hour IOP-lowering effect comparable to that of the established timolol–latanoprost combination, with a less pronounced adverse effect on cardiovascular parameters [27–28].

Intrinsic sympathomimetic activity

Intrinsic sympathomimetic activity (ISA) is a distinctive pharmacological property of carteolol that is not shared by most other topical ophthalmic β -blockers. It refers to partial agonist activity at β -adrenergic receptors despite concurrent receptor blockade. Because carteolol competes with endogenous catecholamines such as epinephrine

and norepinephrine, the degree of receptor stimulation it produces is substantially weaker than that induced by these endogenous agonists. Clinically, this partial agonist activity is associated with less pronounced resting bradycardia and a smaller reduction in cardiac output than with β -blockers lacking ISA. Carteolol has also been reported to have a more favorable metabolic profile, with less marked effects on lipid and glucose metabolism [29–32], as well as a less pronounced impact on respiratory parameters in patients with asthma [33, 34].

Preservative-free formulation

In recent years, increasing attention has been paid to the ocular surface safety of topical ophthalmic medications [35]. Long-term treatment may contribute to iatrogenic ocular surface disease (OSD), most commonly dry eye disease (DED). Because glaucoma therapy is typically lifelong, prolonged exposure to preservatives – particularly benzalkonium chloride (BAK), the most widely used ophthalmic preservative – may induce or exacerbate DED. BAK has been shown to accumulate particularly within the corneal stroma and to have a prolonged biological half-life in ocular tissues (approx. 20 h in the corneal epithelium and 11 h in the conjunctival epithelium, and 8 h in the corneal stroma). It is then gradually and continuously released into both the tear film and the aqueous humor of the anterior chamber. Subjective symptoms of ocular surface disease include burning, itching, foreign-body sensation, and tearing. On examination, patients may present with conjunctival hyperemia, superficial punctate keratopathy, impaired tear film parameters on diagnostic testing (including TBUT, Schirmer testing, LIPCOF assessment, and tear osmolality), and meibomian gland dysfunction. Long-term use of BAK-containing eye drops may promote conjunctival goblet cell loss and inflammatory changes in the anterior segment, including the conjunctiva, cornea, and trabecular meshwork [36]. Multicenter studies, including the PESO Study [37], have also shown that such ocular surface changes may adversely affect the prognosis and success of glaucoma filtration surgery. Preservative-free 2% carteolol eye drops may help reduce the risk of exacerbating dry eye disease and other forms of ocular surface disease, while improving comfort during long-term topical therapy. Avoiding preservatives may also be beneficial in patients who may require glaucoma surgery in the future. Improved local tolerability may, in turn, support better adherence to treatment and persistence with regular eye-drop use over the long term.

Dosing and prolonged duration of action

The convenience of once-daily dosing is an important factor in supporting both adherence to the prescribed regi-

men and long-term persistence with glaucoma therapy. More complex dosing schedules may increase the likelihood of missed doses and poor adherence, potentially resulting in greater fluctuations in intraocular pressure and, consequently, an increased risk of visual field progression. Poor adherence and reduced persistence, including missed doses and treatment interruptions, are clinically important and relatively common problems among patients with glaucoma [38–40].

Preservative-free 2% carteolol eye drops are formulated with 1% sodium alginate as a viscosity-enhancing vehicle. Alginate is a natural polymer that increases formulation viscosity and ocular surface residence time, thereby prolonging precorneal contact and enhancing ocular bioavailability. Clinical studies have shown that this prolonged-action formulation, administered once daily, provides an IOP-lowering effect comparable to that of conventional 2% carteolol administered twice daily [41, 42]. In addition to improving convenience for the patient, once-daily dosing may also enhance treatment tolerability by reducing exposure to both the active drug and excipients. This may help limit both systemic and local adverse effects associated with the active ingredient itself as well as with formulation components such as pH stabilizers, phosphate buffers, emollients, and surfactants [43].

Studies have shown lower plasma concentrations of carteolol with the prolonged-action formulation, which may translate into a reduced risk of systemic adverse effects [44].

CONCLUSIONS

The characteristics of preservative-free, prolonged-action 2% carteolol outlined above, when considered in the context of other topical β -blockers used in the treatment of open-angle glaucoma, suggest that it may represent a valuable option for initial therapy. Its IOP-lowering efficacy allows this nonselective β -blocker, like timolol, to be used either as monotherapy or in combination with topical agents from other pharmacological classes.

A distinctive pharmacological feature of carteolol is its intrinsic sympathomimetic activity, which may contribute to a more favorable systemic safety profile and may be advantageous in patients with coexisting cardiovascular or metabolic comorbidities. Its prolonged-action formulation provides effective IOP control with once-daily dosing, simplifying the treatment regimen and potentially improving adherence and treatment convenience. The preservative-free formulation additionally reduces chronic ocular surface exposure to preservative-related toxicity during long-term glaucoma therapy.

TABLE 1

Summary of the key characteristics of topical β -blockers available in Poland for the treatment of glaucoma [45–49].

	IOP reduction	Dosing	β -adrenergic receptors blocked	Risk of systemic adverse effects	Intrinsic sympathomimetic activity (ISA)	Reduced adverse effects on the cardiovascular system and on lipid and glucose metabolism
0.5% betaxolol	15–25%	twice daily	β_1	low risk in patients with asthma or COPD	no	no
2% carteolol	20–25%	once daily	β_1, β_2	moderate	yes	yes
0.5% timolol	20–30%	twice daily	β_1, β_2	high	no	no

COPD – chronic obstructive pulmonary disease.

CORRESPONDENCE

Jaromir Wasyluk, MD, PhD

Department of Ophthalmology, Military Institute of Aviation Medicine

01-755 Warszawa, ul. Krasińskiego 54/56

e-mail: jwasyluk@wiml.waw.pl

ORCID

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None.

Ethics:

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