New concepts in steroid glaucoma

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New Concepts in Steroid Glaucoma

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Accepted: 8 August 2023 / Published online: 23 August 2023 © The Author(s) 2023

Abstract
Purpose of Review In this article, we discuss the pathophysiology underlying intraocular pressure elevation associated with corticosteroid use as well as targeted therapies for treatment.

Recent Findings Several signaling pathways at the level of the trabecular meshwork are altered by steroid exposure. A pre-existing diagnosis of glaucoma is the best-established risk factor for development of steroid-associated ocular hypertension. Topical, local, and systemic steroids have all been associated with ocular hypertension.

Summary Current management is directed at steroid-sparing alternatives to treatment, steroid cessation, IOP-lowering medications, and interventional lasers and surgery.

Keywords Secondary open-angle glaucoma · Corticosteroids · Steroid-induced glaucoma · Trabecular meshwork · Intraocular pressure · Uveitis

Introduction
Synthetic glucocorticoids and analogs are commonly used to treat many medical conditions [1]. Specific to the eye, we use steroids to reduce post-procedural inflammation and for inflammatory diseases, such as uveitis. Studies in cellular models and in humans (some of which will be reviewed in this paper) have demonstrated that steroids increase intraocular pressure (IOP). If left untreated, elevated IOP can lead to progressive glaucomatous optic nerve damage and vision loss [2]. This disease entity has been called by several names, including “steroid glaucoma,” “steroid-associated glaucoma,” and “steroid-induced glaucoma.” Recent research has focused on elucidating structural alterations and molecular signaling underlying steroid-induced glaucoma as well as on therapeutics and surgical interventions.

Historical Perspective
Ocular hypertension in patients treated with steroids was first reported in the 1950s [2, 3]. In a 1951 review article describing use of steroids for ophthalmic conditions ranging from allergic conjunctivitis to optic neuritis, the authors noted several cases of ocular hypertension after steroid exposure, but they hedged that the relationship might be coincidental. In 1958, Lester Covell published three cases and definitively warned the reader to the adverse effects of steroids on IOP [4]. Then, in the 1960s, Mansour Armaly at the University of Iowa published several elegant studies demonstrating the hypertensive effect of topical steroids [4, 5]. In a study comparing patients with glaucoma versus those without, he reported that nearly all eyes of patients with baseline IOP of 25–30 mmHg reached an elevated IOP near 40 mmHg within three weeks of steroid exposure. Within three weeks of steroid withdrawal, IOP decreased to pre-exposure levels. A single patient in this group did not have a hypertensive response to steroid. His data showed that the hypertensive response was greater in eyes with glaucoma compared to those without. Additionally, he demonstrated that pilocarpine, epinephrine, and acetazolamide successfully lowered IOP in eyes with steroid-induced hypertension; however, steroid use could still induce hypertension in eyes concurrently treated with IOP-lowering medications. In these publications, he also conjectured that steroids could unmask a predisposition for glaucoma in patients with a family history of glaucoma. Dr. Armaly’s work continues to be the cornerstone for research related to steroid glaucoma.
Pathophysiology

Decades of research have reproducibly demonstrated that steroids are associated with increased outflow resistance in the pressure-dependent pathway. Since the 1960s, electron microscopy has been used to demonstrate thickening of the trabecular meshwork with alterations in glycosaminoglycans in eyes treated with steroids. In these post-mortem and in vitro studies, it could not be determined whether alterations of the trabecular meshwork were a cause or a result of elevated intraocular pressure or simply an association with exposure to steroid [6–8]. Protein assays further demonstrated altered levels of specific glycosaminoglycans in eyes treated with steroids compared with control eyes [9]. In addition to glycosaminoglycans, other components of the extracellular matrix (e.g., actin) have been implicated in decreased permeability of trabecular meshwork treated with steroid [10, 11]. Phagocytosis and autophagy have also been shown to be dysregulated in steroid-exposed trabecular meshwork [12•].

Several protein signaling pathways have been studied in tissue culture and animal models. Rho-associated protein kinase (ROCK) signaling contributes to cytoskeletal remodeling in steroid-treated trabecular meshwork, and ROCK inhibitors reverse this remodeling [13, 14•, 15]. A long-noncoding RNA called ANRIL and the p15 gene are differentially expressed in mice with steroid-induced glaucoma, and it has been proposed that ANRIL/p15 control of TM cell senescence has a role in the pathophysiology of steroid-induced glaucoma [16]. Aside from their role in pressure-independent uveoscleral outflow, prostaglandins might increase TM outflow [17]. Transforming growth factor β (TGFβ) signaling has also been implicated [18].

With an increase in minimally invasive glaucoma surgery, steroid-associated IOP elevation has been reported following excision of the trabecular meshwork (i.e., goniotomy), suggesting steroids might additionally alter the pressure-independent pathway [19]. Alternatively, remnants of the trabecular meshwork that persist after trabecular meshwork excision might still play a role in control of the intraocular pressure.

Epidemiology

Studies do not demonstrate one hundred percent incidence of ocular hypertension after steroid exposure; in other words, not all eyes are steroid-responders. A history of glaucoma is the best-established risk factor for a predisposition to steroid-associated ocular hypertension. In Armaly’s early work, eyes with pre-existing glaucoma had higher incidence and higher magnitude of IOP elevation following exposure to topical steroids [4, 20]. In a study of 929 eyes undergoing intravitreal triamcinolone injection, eyes with pre-existing glaucoma were more likely to develop elevated IOP after steroid injection [21].

Several retrospective studies report an association of steroid-associated ocular hypertension with younger age and axial length [22, 23]. There are likely many confounders and uncontrolled variables due to the retrospective nature of these studies, such as the nature of the underlying disease/surgery, dosing versus body size, and ocular angle anatomy.

Route of Administration

Armaly’s historical studies provide strong evidence for the IOP-elevating effect of topical steroids. There is a multitude of heterogeneous evidence—ranging from case reports to clinical trials—demonstrating the hypertensive effect of steroids administered into the vitreous, intranasally, orally, and intravenously [24].

Intravitreal

Elevated IOP following intravitreal injection of steroid is well described in case series and randomized controlled trials. Singh et al. published three cases that developed elevated IOP within one week of intravitreal triamcinolone that all required surgical intervention for IOP-lowering [25]. The Standard of Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) Study compared doses of intravitreal triamcinolone with laser/observation in 682 patients with macular edema from retinal vein occlusions [26]. Eyes with a history of glaucoma were excluded, and management of elevated IOP was at the discretion of the treating physician during the study. In the SCORE study, a 1 milligram dose of intravitreal triamcinolone conferred an increased risk of IOP elevation compared with laser/observation, and a 4 milligram dose of intravitreal triamcinolone conferred an even higher risk of IOP elevation. In this study, the median time to elevated IOP was approximately 1–2 months after injection of intravitreal steroid. The GENEVA Study Group compared an intravitreal steroid implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA) with sham in 1267 eyes with macular edema from retinal vein occlusions [27]. In this study group, elevated IOP was shown to occur significantly more in the steroid-treated group, with a peak in IOP change at two months after injection. In this study, five patients required procedural intervention for pressure.
Inhaled

Inhaled corticosteroids have been shown to elevate IOP, but the effect is likely dependent on dosing and length of use [28]. In a large case-control study of more than 35,000 patients, treatment with high dose or chronic intranasal steroids were associated with a diagnosis of glaucoma or ocular hypertension [29]. Many other studies conclude that intranasal and inhaled steroids do not increase intraocular pressure, but these studies are limited by small sample size, variability in dose and length of use, and exclusion of patients with comorbid POAG [30, 31]. Given that not all eyes are steroid responders, the small studies are likely missing steroid responders and limit conclusions that can be drawn.

Systemic

Several studies describe dramatic elevation of IOP in children treated with systemic (oral or intravenous) steroids. In a study of nine babies treated for infantile spasms, five required IOP-lowering treatment after initiating systemic steroids [32]. In a study of 33 children treated with oral prednisone for autoimmune hepatitis, 20 developed elevated IOP by one month [33]. In another study of 37 children treated for autoimmune disease, 22 children developed a diagnosis of steroid-induced ocular hypertension [34]. Additionally, there are multiple published case reports of IOP elevation developing after initiation of systemic steroids. Elevated intraocular pressure has also been reported after intraarticular steroid injections [35].

One of the challenges in studying the effect of steroids on IOP is that the comorbidities in eyes treated with steroids can also contribute to IOP elevation and glaucoma. For example, intraocular inflammation can elevate IOP (e.g., herpetic) and can cause aqueous outflow dysregulation due to synechiae. Also, there is moderate evidence that intravitreal injections of non-steroidal medications are a risk factor for elevated IOP, so it is important to consider both the pharmacological effect of steroid and the mechanical effect of the injection when determining the risk of intravitreal steroid injections [36].

Management

The first step in management of steroid-induced ocular hypertension is to eliminate the offending agent. It is important to involve the patient’s care team (e.g., primary care physician, rheumatologist, otolaryngologist) to determine if an alternative steroid-sparing therapy can be used in place of systemic or inhaled steroids. When an ophthalmic steroid is the culprit, alternatives such as non-steroidal anti-inflammatory drugs (NSAIDs) and anti-VEGF agents should be considered for inflammation and/or macular edema. For post-operative ophthalmic steroids in patients with glaucoma, we recommend either topical steroids (that can be tapered) or injection of a depot that can be removed (e.g., subconjunctival triamcinolone) instead of a depot that cannot be easily removed (e.g., intra-punctal insert). In cases where the steroid cannot be withdrawn topically, there are different types of glucocorticoids to consider.

If medically appropriate, we recommend fluorometholone (FML) in cases where there is an elevated response to other agents. Multiple studies demonstrate that FML does not elevate IOP to the same extent that dexamethasone does, possibly because FML penetrates the eye less than other topical steroids [37–40].

Medical management of steroid-induced IOP elevation includes all the IOP-lowering agents used for primary open-angle glaucoma. Netarsudil is a ROCK inhibitor that was approved by the FDA in 2017. In anecdotal reports, netarsudil can lower IOP in steroid-associated glaucoma refractory to other medications, perhaps by modulating trabecular outflow that has been dysregulated by steroids [41]. From 2009 to 2012, several published studies (including a randomized clinic trial) discussed anecortave acetate as a possible treatment for steroid-induced IOP elevation [42, 43]. Anecortave acetate is a synthetic compound derived from cortisol but without glucocorticoid activity. As far as we are aware, there has been no more recent development published on the use of anecortave acetate for IOP.

Interventional treatment of steroid-induced IOP elevation includes selective laser trabeculoplasty (SLT) and surgery. SLT directly targets the dysregulated trabecular meshwork. Although SLT can cause intraocular inflammation, SLT has been successful for IOP lowering in eyes with quiescent uveitis [44]. Surgical options for steroid-induced glaucoma include angle-based surgery and/or trabecular bypass surgery. For example, goniotomy has been found to be effective in eyes with steroid-induced glaucoma [45, 46]. Trabecular bypass surgery is also an important tool for management of steroid-induced glaucoma, particularly tube implants for patients with uveitis and refractory elevated IOP. We prefer a valved tube in uveitic glaucoma patients given markedly elevated pre-treatment IOP and risk for long-term hypotony. There still remains little surgical data on glaucoma outcomes for patients with uveitic glaucoma and/or steroid-induced glaucoma.

Conclusion

Steroids continue to be an important treatment for inflammation control and immunosuppression in the eye. Steroids are also a risk factor for increased IOP and development of
glaucoma. From decades of research, underlying structural changes at the level of the trabecular meshwork are now better understood. Current research focuses on targeted therapeutics. Physicians prescribing steroids need to be prepared for close monitoring of IOP and modifications to treatment plans to adequately care for these patients.

Compliance with Ethical Standards

Conflict of Interest Erin Sieck has served on an Advisory Board and received an honorarium for participation for Allergan. Ariana Levin declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance
- Of importance

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