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## Review Article

## Corticosteroid-induced Glaucoma: An avoidable blindness

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## ABSTRACT

Healthcare professionals frequently advise the use of topical steroid eye drops to manage and control postoperative inflammation following phacoemulsification. Although there are many benefits associated with steroid usage, it is imperative to recognize the potential negative repercussions that may arise. In individuals who respond to steroids, the use of topical steroid drops can lead to an increase in intraocular pressure (IOP). Increase in IOP resulting from the side effects of steroids typically manifests several weeks following the initiation of eye drop therapy. The first documentation of steroid induced glaucoma (SIG) can be traced back to the 1950s on the administration of systemic adrenocorticotropic hormones. The elevation of IOP is a complex issue influenced by various factors, but the primary factor is the increased resistance within the outflow mechanisms of the trabecular meshwork. Out of all the risk factors related to ocular hypertension caused by steroid use, a preexisting glaucoma diagnosis is the most frequently seen. The usage of different routes of steroids administration has been linked to the occurrence of ocular hypertension. The current management approach prioritizes the exploration of steroid-sparing treatment options, discontinuing steroid use, employing medications to lower intraocular pressure, and considering interventional laser and surgical procedures.

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## 1. Introduction

Using steroids as a treatment option for autoimmune besides inflammatory conditions is widespread, resulting in doctors frequently prescribing them to patients.<sup>1</sup> Healthcare professionals frequently advise the use of topical steroid eye drops to manage and control postoperative inflammation following phacoemulsification.<sup>2</sup> Elevated intraocular pressure (IOP) is a side effect of administering topical steroids. The persistence of ocular hypertension over an extended period can lead to an heightened stake of developing steroid induced glaucoma by damaging the optic nerve.<sup>3</sup> The earliest documented case of steroid induced glaucoma (SIG) dates back to the 1950s, when systemic adrenocorticotropic hormones were administered.<sup>4</sup> Having

devoted four years to research, Francois presented a comprehensive report on the initial manifestation of increased IOP resulting from the local application of steroid drops.<sup>5</sup> This secondary glaucoma fascinated researchers, as it has the potential to reveal the intricate mechanisms that contribute to open angle glaucoma.

The elevation of IOP is a complex issue influenced by various factors, but the primary factor is the increased resistance within the outflow mechanisms of the trabecular meshwork (TM). By introducing steroid drops, cross-connecting can be induced in the network, enabling alterations to the microstructure of the actin fiber chain.<sup>6</sup> Another potential cause could be elevated collagen and fibronectin within the extracellular matrix of the juxta-canalicular region, leading to increased accretions.<sup>7</sup> The influence of topical steroids on the turnover of constituents

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and enzymes in the TM leads to an escalation in outflow resistance within this fundamental regulatory constituent of IOP levels.<sup>8</sup> There are many situations where individuals have the choice to opt for nonsteroidal alternatives rather than resorting to steroids. Where attaining this is improbable, it becomes vital to monitor the intraocular pressure (IOP), regardless of the steroid's usage. To prevent vision-related complications, particularly in children, timely intervention is imperative when dealing with the ocular hypertensive response.

## 2. Etiology

Susceptible individuals who have administered steroids may experience the occurrence of ocular hypertension (OHT). The elevation of IOP in cases of SIG can give rise to irreversible optic neuropathy.

Several definitions for steroid responsiveness have been put forth over the years. Various thresholds can be employed when evaluating elevated IOP. A raise in IOP greater than 5 mm Hg, an IOP above 21- or 24-mm Hg, an IOP increase greater than 5 mm Hg with values above 24 mm Hg, or an IOP increase greater than 10 mm Hg over baseline with clinical significance. The last definition is the most widely accepted.<sup>9,10</sup>

Steroid responders experience IOP elevations, and this is most observed after the administration of steroids through topical, periorbital, and intraocular routes. It is worth emphasizing that OHT might arise after the administration of substances through intranasal, inhalational, systemic, and dermatological routes.<sup>11</sup>

Medical professionals noted an elevation in IOP within 3 to 6 weeks after the use of steroid eye drops. It is possible that it happened at a previous juncture. Normally, it takes about two weeks for IOP to return to normal following the discontinuation of steroid usage. Conversely, there is a possibility of a rapid elevation in IOP because of corticosteroid eye injections.<sup>12</sup> Using alternative routes for glucocorticoid administration may influence IOP.

## 3. Epidemiology

The specific occurrence of secondary glaucoma in relation to other types remains unclear. The normal population experiences a nonresponse rate of approximately 61 to 63% with GC, which leads to IOP elevations below 5 mm Hg. In comparison, around 33% of the general population shows a moderate response, where IOP levels increase between 6 to 15 mm Hg. Conversely, a highly responsive subset of four to six percent showcases IOP elevations exceeding 15 mm Hg.<sup>13</sup> Conversely, the application of steroid eye drops resulted in a significant elevation of IOP in forty-six to ninety-two percent of patients diagnosed with POAG.<sup>14</sup>

The incidence of a steroid response in children is comparable to that observed in the general adult population,

and there is evidence suggesting a greater occurrence of this phenomenon in pediatric patients.<sup>15,16</sup> Children experience the onset of steroid response sooner and witness a more rapid progression compared to adults, resulting in an elevated IOP in some individuals after only one day of taking glucocorticoids. Recent findings have shown the upsurge in rate of SIG in children, entailing an escalation in the unmonitored use of topical steroid eye drops.<sup>17</sup>

### 3.1. Predisposing factors

Despite limited understanding, experts have identified various factors that play a role in the development of SIG. Presented below are several factors that have been enumerated.

#### 3.1.1. History of primary open angle glaucoma

A four-week treatment with topical steroid drops may lead to an increase in intraocular pressure in around ninety percent of patients with POAG.<sup>14</sup> Individuals classified as high steroid responders within the general population have a higher incidence of POAG. Having first-degree relatives with POAG increases the likelihood of being classified as steroid responders.

The specific causes behind the elevated level of steroid responsiveness in individuals with glaucoma, in contrast to the general population, remain unclear at present. One explanation for this could be attributed to the distinct expression patterns exhibited by the two GR isoforms, namely GR $\alpha$  and GR $\beta$ . The comparison between TM cells detached from glaucomatous eyes and TM cells secluded from individuals without health issues revealed a significant difference in the levels of GR $\beta$ , with the former showing notably lower levels.<sup>18,19</sup> The GR $\beta$  isoform functions as an endogenous dominant negative inhibitor of GR $\alpha$ -mediated transactivation of glucocorticoid-responsive genes.<sup>20</sup>

#### 3.1.2. Age

Age is also regarded as a contributing factor to risk. Children under the age of ten show a significant increase in IOP in response to the usage of steroids drops, placing them at the highest risk for glaucoma.<sup>21</sup> About 25% of acquired glaucoma cases in children can be attributed to this specific subtype.<sup>22</sup> For children, the rise in IOP and the potential glaucomatous damage that may follow can begin earlier, exhibit greater severity upon presentation, and show a more rapid progression in contrast to adults.<sup>20</sup> The vulnerability is higher among the geriatric demographic, as well as children under six years old. Older individuals have a greater likelihood of experiencing a surge in IOP after receiving steroid eye drops. The calculated odds ratio for glaucoma development in geriatric patients managed with topical steroid drops was found to be 1.72.<sup>23</sup> The researchers of the Multicenter Uveitis Steroid Treatment Trial reported that individuals under the age of 50 were

identified as one of the risk factors linked to an increase of 10 mm Hg or more in IOP in eyes with uveitis treated with intravitreal implant of fluocinolone acetonide.<sup>24</sup> With ocular hypertension, the impact of topical steroids is observed to be significantly greater in children than in adults, and there are various factors that contribute to this disparity. Among these factors, the underdeveloped trabecular meshwork is widely recognized as the most influential.

### 3.1.3. Other predisposing factors

Multiple authors have suggested a genetic predisposition for corticosteroid glaucoma.<sup>3,14</sup> According to existing literature, patients suffering from particular connective tissue diseases, type I diabetes, or progressive myopia exhibit a heightened vulnerability to steroid response.<sup>13,25–30</sup> Other effects that have been documented include an increase in corneal thickness and a slight dilation of the pupils. There is no evidence to support a link between these changes and ocular hypertension.<sup>31,32</sup> Patients who have pigment dispersion syndrome, traumatic angle recession, or endogenous hypercortisolism are more susceptible to corticosteroid response.<sup>30</sup>

## 4. Routes of Steroid administration

### 4.1. Topical route

In addressing conjunctivitis, allergies, ocular inflammations, and post-laser and surgery recovery, healthcare providers often turn to topical steroids as an effective treatment option.<sup>33</sup> Self-administered topical steroids can explain the high incidence of SIG in both children and adults. Increases in IOP ranging from 6 to 22 mm Hg can persist for several months following treatment. The application of topical steroid drugs has been linked to a documented rise in IOP.<sup>34</sup> It is recommended to opt for newer topical formulations that exert a reduced influence on IOP. Elevated IOP can endure for a period of up to 18 months after the cessation of topical therapy.<sup>35,36</sup>

### 4.2. Intraocular route

Intraocular steroid usage has significantly increased over the past decade. This pertains to the utilization of intravitreal injections or implants to treat choroidal, macular, and retinal complications.<sup>33</sup> Fluocinolone is more often linked to SIG, while dexamethasone presents reduced risks with intravitreal injections.<sup>34</sup> The occurrence of SIG can range from 11% to 37% when these drugs are used, and in combination with uveitis, it may increase to as high as 79%.<sup>35</sup> Over the course of a few weeks, there is a discernible increase in IOP, reaching its maximum at 7 months, followed by a subsequent decrease after three to four months.<sup>36</sup>

### 4.3. Periocular route

In steroid responders, the sub-tenon space is the preferred periocular routes, although it presents a higher risk of SIG as it is situated close to the anterior chamber angle.<sup>37</sup> An investigation conducted across multiple centers examined the impact of diverse periocular cortisone treatments on uveitis patients. The study revealed that roughly 35% of individuals experienced an increase in IOP exceeding 24 mm Hg, with 2.4% of them requiring glaucoma surgery.<sup>38</sup>

### 4.4. Systemic route

For a multitude of chronic inflammatory diseases, the standard course of treatment involves the prescription of systemic steroids. The likelihood of SIG occurring is decreased when systemic therapy is used instead of ocular treatment. Patients who undergo prolonged systemic steroid treatment may experience a notable increase in IOP, which can persist for years.<sup>39</sup> Based on findings from various studies, some observe that systemic cortisone has been prescribed to approximately 20% of individuals suffering from glaucoma. These patients showed a decline in their visual perception.<sup>40</sup>

### 4.5. Inhalational route

A clear link has been established between the utilization of inhaled steroids and the development of ocular hypertension, with the risk amplifying in patients with a familial predisposition to glaucoma, particularly with escalated dosage and frequency of administration. The IOP-elevating effect was hypothesized to occur because of the systemic absorption of the drug or from a poor administration technique that can lead to the direct entry of the drug into the eye.

## 5. Duration of steroid use

In patients who respond to steroids, an increase in IOP typically occurs within the initial weeks of steroid treatment. The elevation can occur within an hour or extend over many years following the chronic administration of steroids. The normalization of intraocular pressure usually occurs within four weeks after the discontinuation of steroid medication.

## 6. Pathophysiology

Many studies have observed a correlation between steroids and increased outflow defiance in the pressure vulnerable channel. The conclusive establishment of the association between TM changes, elevated IOP, and steroid exposure was not possible based on the findings of in-vitro studies.<sup>41–43</sup> Examination of protein assays showed marked variations in the quantities of specific glycosaminoglycans in eyes that received steroid treatment when compared to control eyes.<sup>44</sup> Besides glycosaminoglycans, other

elements of the extracellular matrix have been linked to the diminished permeability of steroid-treated trabecular meshwork.<sup>45</sup> In the trabecular meshwork, dysregulation of phagocytosis, as well as autophagy, has been found to occur because of steroid exposure.<sup>46</sup>

Several proteins 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.<sup>47–49</sup> The differential expression of the long-noncoding RNA ANRIL and the p15 gene has been observed in mice with steroid-induced glaucoma, leading to the proposal that ANRIL/p15 control of TM cell senescence contributes to the pathophysiology of this condition.<sup>50</sup> Aside from their role in pressure-independent uveoscleral outflow, prostaglandins might increase TM outflow.<sup>51</sup> Transforming growth factor  $\beta$  (TGF $\beta$ ) signaling has also been implicated.<sup>52</sup>

## 7. Clinic Features

Patients frequently exhibit symptoms reminiscent of those found in individuals with POAG, with the presentation of these symptoms varying based on age. The presentation of congenital glaucoma in newborns may involve symptoms such as increased tear production, contractions of the eyelids, and heightened subtlety to light. Characteristics displayed by teenagers are in line with developmental POAG. Among adults, it is common to observe heightened IOP, unobstructed angles during gonioscopy, optic disc cupping, and impaired vision. The administration of steroid eye drops in individuals diagnosed with vernal keratoconjunctivitis (VKC) frequently results in the emergence of SIG.<sup>53</sup>

## 8. Evaluation

Upon inspection, there are usually no notable findings in the eye. The patient's IOP rises above the standard range of 10 mm Hg to 22 mm Hg, and upon investigation of their steroid usage history, it is revealed that the patient has developed hypertension induced by steroid use. Tonometry is a necessary instrument for diagnosing SIG, as it is for all varieties of glaucoma.<sup>54</sup>

By examining the patient's medical history, we may uncover potential factors contributing to this condition. Individuals afflicted with various forms of allergic conjunctivitis may employ prolonged use of steroid eye drops. Steroid eye drops may be administered to patients for postsurgical conditions like Photorefractive Keratectomy, or they may have an embedded depot steroid. Another subgroup at increased risk for glaucoma comprises individuals who have undergone renal transplantation. The assessment encompasses several components, and they are listed below.

1. Recording visual acuity,
2. Examination of the anterior and posterior segments,
3. Tonometric assessment,
4. Ocular coherence tomography (oct) testing,
5. Gonioscopy.

## 9. Management

The initial measure in managing steroid-induced ocular hypertension involves discontinuing the causative agent. The involvement of the patient's care team is crucial in determining the feasibility of substituting systemic or inhaled steroids with an alternative steroid-sparing therapy. Where an ophthalmic steroid is the cause, it is recommended to explore alternatives like non-steroidal anti-inflammatory drugs (NSAIDs) and anti-VEGF agents to address inflammation and/or macular edema. In patients with glaucoma undergoing post-operative ophthalmic steroid treatment, we advise the use of either tapered topical steroids or the administration of a removable depot instead of an irremovable depot. When topical steroid withdrawal is not achievable, it is important to consider different varieties of GC.<sup>55</sup>

The three modes of management of SIG are:

### 9.1. Medical management

Beta-blockers are the most commonly prescribed drug in SIG.<sup>1</sup> In 2017, the FDA granted approval to Netarsudil, a ROCK inhibitor. Based on anecdotal evidence, netarsudil has shown efficacy in lowering IOP in cases of steroid-associated glaucoma that are unresponsive to alternative medications.<sup>56</sup> Between 2009 and 2012, anecortave acetate provided promising results in managing SIG.<sup>57,58</sup> Derived from cortisol, anecortave acetate does not possess glucocorticoid activity. As far as we are aware, there has been no more recent development published on the use of anecortave acetate for IOP. Multiple studies reveal FML has a diminished ability to raise IOP compared to dexamethasone, possibly because of its limited ocular permeability relative to other topical steroids.<sup>55</sup>

### 9.2. Laser trabeculoplasty

Where antiglaucoma drugs are ineffective, implementing Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) is recommended for the management of SIG. SLT specifically focuses on the dysregulated trabecular meshwork. Despite the potential for intraocular inflammation, SLT has proven effective in reducing IOP in eyes with quiescent uveitis.<sup>59</sup>

### 9.3. Surgical management

Surgical intervention is recommended for patients who do not show improvement in medical and laser treatments.

It may also be advisable for individuals who are likely to receive ongoing steroid treatment. Angle-based surgery and/or trabecular bypass surgery are among the surgical options available for treating glaucoma induced by steroid usage.<sup>55</sup> Trabeculectomy is the surgical procedure most frequently used. Among the choices are deep sclerectomy, canaloplasty, tube shunt surgeries, or cyclophotocoagulation procedures.<sup>1</sup>

## 10. Differential Diagnosis

In patients with POAG, it is necessary to consider whether the increase in IOP after surgical management is because of a steroid-induced response. Diagnostic challenges may also arise in individuals who do not have a prior glaucoma diagnosis but use steroids. Determining the exact cause of increased IOP in uveitic glaucoma patients can present considerable difficulties, and in certain cases, may be deemed an unattainable goal.<sup>60,61</sup> Besides receiving long-term steroid treatment, these eyes frequently display elevated IOP because of various mechanisms, such as angle closure, acute or chronic trabecular damage, and reduced trabecular outflow.<sup>62</sup>

Particularly in cases of trabeculitis, the level of anterior segment inflammation may not accurately reflect the extent of IOP elevation, making diagnosis difficult. The clinical presentation of uveitic glaucoma patients becomes more intricate because of intermittent reduction of intraocular pressure (IOP) caused by decreased aqueous production from the inflamed ciliary body.<sup>62</sup> Another potential factor may explain the observed decrease in IOP. This factor involves the promotion of uveoscleral outflow, which is facilitated by endogenous prostaglandins induced by inflammation.<sup>62</sup>

Both blunt and infiltrating eye injuries in patients who have been treated with steroids can create challenges in making a diagnosis.<sup>63</sup> Individuals who have experienced violent ocular surface chemical burns may display a steroid-caused response, besides elevated IOP caused by considerable sore in the anterior chamber.<sup>64</sup>

In children, steroid-induced IOP elevation or glaucoma should be included in the differential diagnosis and work-up of primary or secondary congenital glaucoma, pediatric uveitic glaucoma, or aphakic and pseudophakic pediatric glaucoma.<sup>65</sup>

## 11. Conclusion

The development of glaucoma because of steroid use is a preventable condition that is caused by medical intervention. The inappropriate and illogical administration of steroids, particularly in developing nations by local healthcare providers and unsupervised usage by patients, shows a lack of knowledge regarding the condition. Through implementing a few basic precautions, the onset

of SIG can be prevented effectively. Despite notable advancements in recent years regarding the comprehension of corticosteroid-induced glaucoma mechanisms, additional research is necessary. It is expected that a comprehensive comprehension of the response induced by steroids may yield innovative therapeutic approaches for various forms of glaucoma, such as POAG.

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None.

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None.

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