

# Corticosteroid-induced glaucoma in children

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## Abstract

Corticosteroid-induced ocular hypertension is a known entity in adults; however, there is limited information regarding this phenomenon in children. This is of great importance as children are less likely to voice their concerns and likely to present when there are advanced ocular complications. It is also known that intraocular pressure responses due to corticosteroid use are exaggerated in children. In addition, monitoring of intraocular pressure in children is usually more difficult than in adults; and there is still debate on what is the most accurate and effective mode of measuring intraocular pressure. This review aims to present an overview on the currently available literature on corticosteroid-induced ocular hypertension in children with respect to different steroid preparations, anatomic factors and measurement controversies. Guidelines about the use of topical corticosteroids in Chinese children may help in clinical management when this common medication is used.

## Introduction

Corticosteroids are commonly used as anti-inflammatory agents. As early as 1949, numerous scientists including Hench et al<sup>1</sup> proved the efficacy of these drugs in the treatment of rheumatoid arthritis. In a subsequent paper published by Woods,<sup>2</sup> a case of nongranulomatous uveitis associated with rheumatoid arthritis successfully treated with topical cortisone was reported. Since then, the potency and

efficacy of steroids in the treatment of ocular inflammation have been well proven and steroids have been widely used in various ocular conditions such as severe allergic conjunctivitis, uveitis and postoperative inflammation. However, the use of corticosteroids is a double-edged sword. Indiscriminate use can lead to a myriad of ocular side-effects, the most common of which is elevated intraocular pressure (IOP). Other known side-effects include cataract, corneal epitheliopathies, exacerbation of infection, ptosis, orbital fat atrophy, venous occlusion and systemic glucocorticoid suppression.<sup>3</sup>

The ocular hypertensive response in adults to oral,<sup>4</sup> intravenous,<sup>5</sup> topical dermatologic,<sup>6</sup> topical ocular<sup>7,8</sup> and periocular corticosteroids<sup>9,10</sup> is well established. Even inhalation and nasal corticosteroids<sup>11</sup> have been reported to be associated with ocular hypertension in susceptible adults. Case reports of elevated IOP from intravitreal corticosteroid injections for a variety of posterior segment disorders have also been published.<sup>12,13</sup>

Systemic application of corticosteroid in children can have metabolic, musculoskeletal, dermatologic, hematologic and ophthalmologic effects.<sup>14</sup> Its usage in children is associated with a number of ocular side-effects. Hayasaka et al<sup>15</sup> reported that children with nephrotic syndrome who receive corticosteroid treatment may have ocular hypertension, epiblepharon, cataract, hordeolum and bacterial conjunctivitis. Cataract was reported in some children using inhaled corticosteroid.<sup>16</sup> A case of buphthalmos was also reported in the literature.<sup>17</sup> The use of systemic corticosteroid in infants can also lead to a rise in IOP, especially when high dosages are used.<sup>17,18</sup> Nonetheless, there are limited data available, but a lot of controversy, regarding corticosteroid-induced glaucoma in children using topical ocular medications.<sup>19,20</sup>

## Clinical hurdles: intraocular pressure measurement in children

The presence of elevated IOP in children is particularly worrisome. Clinically, glaucoma is symptom-free until significant damage has been done to the eye. Children may not be able to effectively communicate about symptom changes, and in particular, measurement and monitoring of IOP in children is much more difficult than in adults. By no means should the disease reach an advanced and irreversible stage and, thus, should be prevented and treated early.

Accurate, simple and non-invasive measurement of IOP in children remains a major challenge. This might be one of the difficulties in conducting studies on corticosteroid-induced ocular hypertension in children. The commonly used methods for measuring IOP in children include Goldmann applanation tonometry and electronic Tonopen XL (Reichert Technologies, New York, USA).<sup>21</sup> However, pediatric patients may become apprehensive when instruments are applied directly to the cornea despite administration of topical anesthetics.<sup>22</sup> It is not uncommon for a child to struggle and resist the measurement of IOP in clinical settings. Evidence suggests that vigorous resistance to IOP measurement may produce a Valsalva effect, thereby, resulting in an increase of systemic venous pressure.<sup>21</sup> Previous studies have shown that contact between the eyelashes or eyelids and the applanation prism can increase IOP.<sup>23</sup> A recent study by Gandhi et al<sup>24</sup> demonstrated that attempted forced eyelid closure is a common and statistically significant source of error in routine outpatient measurement of IOP, using both Goldmann tonometry and Tono-pen. Gandhi et al<sup>24</sup> suggested that neither instrument is particularly more effective than the others for use in the uncooperative patient. Another study by Epley et al<sup>25</sup> showed that the use of an eyelid speculum increased IOP by an average of 4 mm Hg. Although sedation may be used for IOP measurement, the risk of adverse effects arising from the process of sedation itself may pose a problem in certain susceptible children.

An ideal device for IOP measurement should be accurate, reliable, safe, simple to use, inexpensive and acceptable to the patient. With the introduction of noncontact tonometry (NCT), the measurement of IOP in children has become more feasible<sup>26</sup> and may offer a good alternative to older methods of IOP measurement. According to a study by Jaafar and Kazi<sup>27</sup> in which they measured IOP in 620 eyes, they concluded that the NCT was a highly accurate and reliable test. It agreed very closely with Goldmann applanation tonometry in which the population IOP mean only yielded a difference of 0.3 mm Hg between the two modalities. More recently, the Icare (Icare Finland Oy, Helsinki, Finland) tonometer has been introduced into the market and has been well received by practitioners. It enables measurement of IOP without the use of local anesthetic, and its portability, ease of use and speculum-free nature were perfect for measuring IOP in young children. Manufacturer data quoted a mean paired difference of

-0.4 mm Hg and standard deviation of 3.4 mm Hg compared with the Goldmann applanator.<sup>28</sup> This can potentially improve the feasibility of future research on corticosteroid-induced ocular hypertension in children.

## Corticosteroid preparation and intraocular pressure responses

Corticosteroids have been known to cause IOP elevation through all modes of administration.<sup>29</sup> Common routes of ocular steroid administration are summarized in **Table 1**. Another factor that determines the potency of the steroid is its chemical structure. Acetates are more lipophilic and permeate the cornea better than phosphates which are relatively hydrophilic; hence, it would be expected that dexamethasone acetate 0.1% can cause greater rise in IOP than other kinds of preparations. **Table 2** summarizes the IOP elevation associated with different corticosteroid strengths.<sup>30</sup>

The rise in IOP can occur within days or weeks in topical preparations, in both normal and glaucomatous eyes.<sup>30</sup> This spike is usually transient and abates with cessation of therapy. Bernstein and Schwartz<sup>31</sup> have noted in their paper that long-term systemic therapy is associated with greater increase in IOP and that longer duration of use was associated with significantly higher IOP.

Although ocular hypertensive response to various steroids used in the adult population has been well reported, only limited information about the drug effect in children is available. A major confounding issue is that, among the few published studies, the results do not concur with each other.<sup>19,20</sup> A study by Ohji et al<sup>19</sup> concluded that the ocular

**Table 1. Ocular steroid preparations**

Topical application	Ocular / periocular injection	Systemic
Drops	Subconjunctival	Oral
Ointments/gel	Subtenon	Intramuscular
Impregnated collagen shields	Peribulbar/retrobulbar	Intravenous
Impregnated contact lens	Intravitreal	-
Liposome preparations	Slow-release devices	-
	Intralesional	

**Table 2. Intraocular pressure elevation with different corticosteroid strengths<sup>30</sup>**

Preparation	Mean ( $\pm$ standard deviation) pressure rise (mm Hg)
Dexamethasone 0.1%	22.0 $\pm$ 2.9
Prednisolone 1.0%	10.0 $\pm$ 1.7
Dexamethasone 0.005%	8.2 $\pm$ 1.7
Fluorometholone 0.1%	6.1 $\pm$ 1.4
Hydrocortisone 0.5%	3.2 $\pm$ 1.0
Tetrahydrocortisol 0.25%	1.8 $\pm$ 1.3
Medrysone 1.0%	1.0 $\pm$ 1.3

hypertensive response to topical dexamethasone was more severe in children than in adults. On the other hand, Biedner et al<sup>20</sup> reported an opposite finding. Ohji et al<sup>19</sup> reported that nine (82%) out of 11 Japanese children younger than 10 years of age who underwent strabismus surgery were either high or intermediate responders after instillation of topical dexamethasone 0.1% three times daily. Biedner et al<sup>20</sup> reported contradictory results in Israeli children who received topical dexamethasone 0.1% four times daily for vernal conjunctivitis. Of the 44 children, only five (11%) were intermediate or high responders. A more recent Singaporean study reported that 28.3% of the children with vernal conjunctivitis developed elevated IOP with topical steroids with 5.5% developing glaucomatous nerve damage.<sup>32</sup> These controversial results may be attributed to racial differences.

In a local study published by Ng et al,<sup>18</sup> children undergoing strabismus surgery treated with topical dexamethasone had an ocular hypertensive response in a dose-dependent manner. This effect was seen even with a twice-daily regimen; the authors suggested that twice weekly monitoring of IOP was desirable.

### Anatomical factors and pathophysiology in intraocular pressure elevation

Bernstein et al's study<sup>33</sup> in 1963 was one of the earliest papers to identify that a rise in IOP was due to a decrease in facility of outflow. His hypotheses can be grouped into the following categories: corticosteroid-induced changes in microstructure of the trabecular meshwork; deposition of substances in the meshwork causing increased outflow resistance; and reduced degradation of substances from the meshwork due to inhibition of proteases.<sup>29</sup>

Microstructural changes identified by Clark et al<sup>34</sup> showed that actin stress fibers were reorganized into networks in trabecular cells in the presence of dexamethasone, causing a decrease in outflow facility. They postulated that this phenomenon was mediated via the meshwork glucocorticoid receptors. This effect was reversible once the drug was discontinued.

A study by Wilson et al<sup>35</sup> found that dexamethasone increased glycosaminoglycan, elastin and fibronectin production in cultured trabecular meshwork cells; and the production of glycosaminoglycan further increased as steroid use was prolonged. In children, a mutation in the *MYOC* gene — and, thus, a mutation in the myocillin protein — is known to be associated with juvenile glaucoma and adult primary angle open glaucoma.<sup>17</sup> Myocillin was also shown to be induced in cultured cells exposed to corticosteroids. Myocillin has been proposed in the aetiology of glaucoma for the following reasons: it has high expressivity in trabecular cells in the presence of corticosteroids; the delay in its expression is similar to that for pressure rise in steroid-treated eyes; and the dose required for protein expression is similar to that required to raise IOP.<sup>30</sup> Controversy exists as

to whether the accumulation of these substances also leads to decreased outflow facility as studies using virus-mediated transfer of myocillin in trabecular meshwork cells showed overexpression of the protein and increased outflow facility.<sup>29</sup>

Suppressed phagocytosis, reduced levels of tissue plasminogen activator, stromalysins and other proteases were observed in cultures of human trabecular meshwork cells treated with dexamethasone. Reduction of phagocytic properties of cells via disruption in the arachidonic acid metabolism causes an increase in debris in the trabeculum and, hence, increased resistance to outflow. This effect may be particularly significant in children as their trabecular meshworks are relatively immature with a potentially greater IOP rise when obstruction occurs.<sup>17,18,35,36</sup>

### Topical corticosteroids

Topical steroids remain the most common ophthalmic preparation and mode of administration to the eye. Corticosteroids are detectable in the aqueous humor within 5 to 30 minutes of application.<sup>3</sup> The route of penetration is via the cornea; the greatest barrier is the lipid-rich epithelium. Thus, in the absence of corneal epithelial integrity, as occurs during surgery or after trauma, there is increased penetration of the drug. Higher concentrations are also seen in the presence of ocular inflammation due to surgical<sup>18</sup> or non-surgical causes. However, the data on intraocular penetration of steroid are often varied in their conclusions as drug formulations, mode of delivery, and intraocular measurements may differ according to the methods used such as liquid chromatography, gas chromatography and radioimmunoassays.<sup>37</sup>

Fluorometholone has been known to produce less ocular hypertensive responses compared with dexamethasone because it undergoes local ocular metabolism in the cornea.<sup>38</sup> Newer topical steroids such as rimexolone<sup>39</sup> and loteprednol<sup>40</sup> target this effect and are less prone to induce significant IOP elevation.

Ointments are useful because these provide more sustained release of medication. However, studies have shown that these may produce a lower peak ocular concentration compared with eye drops. Johansen et al<sup>41</sup> hypothesized that due to its prolonged release, a single application of steroid in ointment form results in 25% less overall absorption of steroid compared with drop form. This may be advantageous in children as prolonged release equates to less frequent application, thus, increasing treatment compliance, as well as resulting in less absorption of topical steroid and, hopefully, lower incidence of IOP rise.

However, there are published data regarding ocular hypertensive responses in children using both drop and ointment forms of steroids. Studies by Kass et al,<sup>42</sup> Ohji et al,<sup>19</sup> Kwok et al,<sup>43</sup> Ng et al<sup>18</sup> and Ang et al<sup>32</sup> showed IOP responses in children ranging from elevated pressure to congenital glaucoma, with the responses being more marked

in younger children less than 10 years of age versus those in children above the age of 16. Ang et al<sup>32</sup> also observed that the mean duration of steroid therapy before the detection of glaucomatous damage was approximately  $10.8 \pm 6.9$  weeks.

Application of corticosteroid to the eyelids is also associated with an ocular hypertensive response in children. This can be easily overlooked as these drugs are commonly used in the treatment of eczema in children. Garrott and Walland<sup>44</sup> noted elevated IOP in their case series of three adults who applied steroids to eyelids for the treatment of psoriasis, allergic dermatitis and blepharitis; the IOP did not return to normal in two patients even after cessation of steroid therapy. These findings were echoed in a study by Chua et al<sup>45</sup> in which ocular hypertensive response was observed in a 6-year-old child who applied corticosteroid ointment to his eyelid after levator resection. Both studies postulated that this response was due to direct absorption of the drug via the intact skin or the wound, ointment spillover from the lid margin, or systemic absorption of corticosteroid with distribution to the eye via the circulation. Thus, it was recommended to use a milder form of corticosteroid and perform close monitoring. Furthermore, practitioners who lack expertise or equipment in evaluating glaucoma in children should exercise extreme caution in prescribing corticosteroids to a child.

### Periocular and intraocular preparations — “depot injections”

Intraocular inflammation is uncommon in children; it represents 5% to 10% of all uveitis cases in tertiary referral centers,<sup>46</sup> and the percentage may be even less in Asia. Nevertheless, pediatric uveitis remains a treatment challenge because it can cause sight-threatening complications, if neglected. Cystoid macular edema is one of the major causes of visual impairment. Topical steroid preparations in treating this condition appear to be unsatisfactory, and most clinicians are wary of prescribing oral steroid preparations in view of systemic side-effects.

Periocular injection is one method of depositing a localized concentration of steroid in the eye. In a retrospective case review of 147 children with uveitis by Sijssens et al,<sup>47</sup> eyes treated with periocular steroid injections had frequent IOP elevations and secondary glaucoma than those eyes that did not receive such treatment; however, the number of injections given was not associated with the incidence of elevated IOP. One interesting observation was that children with intermediate uveitis who received periocular injections were more prone to have elevated IOP during a 3-year follow-up compared with those who did not. They postulated that these children may have received more injections or that their trabecular meshwork may have been more damaged due to the severity of uveitis.

It should be noted that periocular injections also have certain inherent risks including globe perforation, choroidal injection, central retinal artery occlusion and extraocular muscle imbalance,<sup>3</sup> in addition to ocular hypertension.

Intravitreal triamcinolone (IVTA) has become a widely accepted alternative to periorbital steroid injections in the treatment of ocular inflammations and is also used for other eye diseases such as diabetic retinopathy, veno-occlusive disease and choroidal neovascularization in adults.<sup>29</sup> Triamcinolone acetonide is a potent anti-inflammatory agent — 35 times more potent than cortisol; its increasing use has direct bearing on the increasing number of ocular hypertensive responses seen in everyday practice. In a meta-analysis by Jonas et al,<sup>48</sup> it was found that over half of the eyes injected with intravitreal preparations of 25 mg had an elevated IOP response, and this was usually seen at 1 to 2 months after injection. Ocular hypertensive responses were more severe in younger patients, as also noted in studies by Shukla et al<sup>49</sup> and Roth et al.<sup>13</sup> All three studies showed that the incidence of IOP elevation was independent of the number of injections given; however, this may be due to reluctance in re-injecting an eye with a previous ocular hypertensive response.

Although the previous studies were mostly based in adult populations, one study has investigated the short-term safety of IVTA for uveitic macular edema in children. In this retrospective noncomparative interventional series by Sallam et al,<sup>46</sup> 16 eyes were given 4 mg IVTA in 0.1 mL. They noted that mean IOP increased from a baseline of 12.56 mm Hg (range, 5-19 mm Hg) to a maximum of 22.62 mm Hg (range, 10-44 mm Hg) during treatment, with a median rise observed in 3 weeks. Although most cases responded to topical ocular hypotensive agents and oral acetazolamide, one case required trabeculectomy. The IOP rise occurred earlier in children than in adults, and the authors recommended that IVTA should be avoided in children who have previously exhibited a corticosteroid-induced elevation in IOP. It is also worthwhile to mention the other major complication observed in this study which was the development of posterior subcapsular cataract at 5 to 16 months after IVTA in four eyes that subsequently required lensectomy.

### Oral and inhalational steroids

Many childhood systemic diseases such as nephrotic syndrome and leukemia require oral steroid as part of the therapeutic regimen, often for an extended period of time. As mentioned previously, children frequently exhibit a more marked ocular hypertensive response to topical and depot steroids, and studies have been conducted to see whether children on systemic steroid therapy exhibit the same response.

In a study by Tham et al,<sup>50</sup> the temporal relationship between steroid treatment and elevation of IOP in a 9-year-old leukemic patient corresponded to the start and cessation of oral steroid. The child was prescribed a dose of 60 mg daily and her IOP rose to 40 mm Hg in only 8 days. Response to multiple ocular hypotensive medications was poor, and her IOP only returned to normal (17 mm Hg) 2 days after cessation of oral steroid. During this time, no symptoms were reported except for a drop in visual acuity from 20/20

to 20/40 when the IOP reached 52 mm Hg.

Elevated IOP was also seen in a Japanese study<sup>15</sup> where an ocular hypertensive response occurred in 20% of the children on oral steroid for nephrotic syndrome. Although elevated IOP responses to oral steroid usually subside on cessation of steroid, in this study, one eye with elevated IOP (30 mm Hg) was refractory to topical ocular hypotensive medications despite cessation of oral steroid therapy and, subsequently, required trabeculectomy.

Nonetheless, controversy still exists as other studies failed to show similar results. Studies from Kaye et al,<sup>51</sup> Mino et al,<sup>52</sup> and Shiono et al<sup>53</sup> have not shown an increased incidence of elevated IOP responses in children on oral steroid treatment.

Few studies have examined the role of inhalational steroids in ocular hypertension in children. A study by Opatowsky et al<sup>11</sup> found that inhalational steroids caused an ocular hypertensive response. However, this finding has not been reproduced in other published studies. In a study conducted by Behbehani et al,<sup>16</sup> children on inhaled budesonide and/or beclomethasone for at least 2 years were not found to have elevated IOP or glaucoma. One confounding issue in this study was that some children were also using oral steroids. In another study by Pelkonen et al,<sup>54</sup> no children on inhaled budesonide for at least 18 months develop elevated IOP, and they concluded that inhaled budesonide up to 800 µg per day for a short duration or 200 to 400 µg per day for long-term use did not cause clinically important IOP increases in children with asthma.

## Management

Although a previous review of corticosteroid-induced glaucoma<sup>30</sup> has suggested that the incidence of irreversible ocular hypertensive response was very low (about 3%), with the vast majority of cases resolving by 4 weeks after cessation of corticosteroids, subsequent prospective

studies have reported a much higher incidence rate. In one case series of 16 patients from Pakistan with vernal keratoconjunctivitis (age of subjects not specified) by Farooq and Malik,<sup>55</sup> 12 (75%) had irreversible IOP rise which did not respond to maximal topical and systemic glaucoma treatment, and eventually requiring trabeculectomy with mitomycin C. Of these 12 patients, 10 (83%) had successful IOP control at 6 months postoperatively but six (50%) required surgery for associated cataract development. Another study from India by Sihota et al<sup>56</sup> included 34 consecutive patients with corticosteroid-induced glaucoma. The mean age of these subjects was 28 years (range, 12-72 years); the most common reason for steroid use was vernal keratoconjunctivitis (n=22, 65%); and the mean duration of steroid usage was about 2 years. After steroid usage was stopped, IOP was controlled in the majority (n=25, 73.5%) with medical treatment only, which was gradually tapered off with time. However, just over a quarter (n=9, 26.5%) still required surgery (type of procedure not specified) for IOP control. All subjects who underwent glaucoma surgery were 20 years old or younger, and most (n=8, 89%) had vernal keratoconjunctivitis. All the patients in this study, whether they required surgery or not, eventually did not require any glaucoma medications at 18 months after stopping steroid usage.

## Conclusion

Corticosteroid-induced ocular hypertensive responses in children should not be taken lightly. As the use of corticosteroid becomes more common, their preparations and modalities of administration become more complex. Children are especially at increased risk of developing glaucoma and other associated complications due to increased difficulty in expressing their symptoms and difficulty in examining them for signs of elevated IOP. Judicious use and prudent evaluation of possible side-effects are warranted. Hopefully, as more studies in this topic come to light, we will be better equipped to help our little patients who may not be easily examined or readily symptomatic.

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