Historical Review of Steroid-Induced Glaucoma

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ABSTRACT

This article briefly reviews the literature of steroid-induced ocular hypertension and glaucoma. An insight in the prevalence, risk factors and pathophysiology of this entity can help the clinicians prevent, monitor and treat this secondary form of glaucoma.

Keywords: Intraocular pressure, Steroid response, Secondary open-angle glaucoma.

INTRODUCTION

Association of steroids and glaucoma was first reported in 1950, when systemic administration of adrenocorticotropic hormone (ACTH) was shown to increase intraocular pressure (IOP). IOP elevation in response to topical steroids was first reported by Armaly and Becker.

Steroid-induced glaucoma is a form of secondary open-angle glaucoma, earlier believed to result only after indiscriminate topical steroid use. Other routes of administration, such as oral, intravenous, periocular, dermatological, intravitreal, intranasal have since been held responsible for this devastating and irreversible visual loss due to ensuing glaucoma. In order of reducing frequency, incidence of elevated IOP is less with intravenous, parenteral, dermatological and inhaled routes of administration.

The disease is specially prevalent in countries where steroid use is rampant in the cases of itchy eyes, vernal, atopic keratoconjunctivitis (Fig. 1) with unscrupulous, unregistered and, quite often, ignorant practitioners of medicine. Owing to the quick relief of the red and itchy eyes, these drugs can be dangerous procured off the shelf on regular basis leading to a state of complete self and unmonitored treatment. Extent of morbidity is compounded considering the fact that this affects mostly young subjects with blind years getting added for a long life expectancy of these younger subjects. Vernal keratoconjunctivitis (VKC) with injudicious use of topical steroids has most commonly been associated with steroid-induced glaucoma. Palpabral variety has been associated in a large series of glaucoma. In a study by Sihota et al mixed variety was most common.

Bonini et al in a long-term review of vernal keratoconjunctivitis recorded a 2% incidence of steroid-induced glaucoma. Other ocular routes of administration of steroids causing glaucoma have been recognized off late, viz intravitreal, subtenon, radial keratotomy and after scleral reinforcement procedure. By far and large, steroid glaucoma escapes detection until late stages, especially in this group of patients, due to coexisting ocular morbidity issues. Unmonitored use of topical steroids after laser in situ keratomileusis in predisposed patients can result in steroid-induced glaucoma.

Steroid use in other ocular conditions like chronic or recurrent uveitis can also result in rise of intraocular pressure (Fig. 2).
DEFINITION OF STEROID RESPONDER

Normal population response to steroids can be graded as nonresponders, responders and super responders. According to a study done by Becker2 in 1965, all primary open-angle glaucoma patients showed IOP rise with administration of topical Betamethasone 0.1%. Among normal individuals also two types of responses were observed: 70% showed small rise of IOP while 30% showed high pressure response to topical steroid administration.

Becker’s Study Design

<table>
<thead>
<tr>
<th>Category</th>
<th>Group IA</th>
<th>Group IIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary open-angle</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>Glaucoma (untreated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring</td>
<td>87</td>
<td>19</td>
</tr>
<tr>
<td>Suspects</td>
<td>98</td>
<td>24</td>
</tr>
<tr>
<td>Volunteers</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

Armaly’s Study Design

<table>
<thead>
<tr>
<th>Category</th>
<th>Armaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Dexamethasone 0.1%</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Response

- **Group IA**: IOP rise of 1.6 ± 2 mm Hg seen in 66% normal population, hypertensive response attained in 2 weeks, maximum in 4 weeks.
- **Group II A**: IOP rise of 10 ± 2 mm Hg seen in 28.8% normal population.
- **Group II B**: IOP rise of ≥16 mm Hg seen in 5% normal population.
- **Group I A and Group I I B**: IOP continued to increase throughout 4 weeks.

Once the steroids were withdrawn, most of the eyes returned to the baseline level within 3 weeks.18 Few cases of irreversible elevation of IOP after subtenon injection of triamcinolone requiring filtering surgery are also reported.19 It has been reported that the elevation of IOP resulting after systemic steroid administration is much less as compared to topical steroids.20

PATHOPHYSIOLOGY

Glucocorticoids decrease the aqueous outflow by unknown mechanism. The most common explanation for this has been accumulation of glycosaminoglycans in the trabecular meshwork by glucocorticoids,23 by stabilizing lysosomal membranes and inhibiting the release of catabolic enzymes. A variety of substances contributing to the extracellular matrix is secreted by cultured trabecular meshwork cells. Treating cultured trabecular cells with steroid induces the secretion of elastin, which may have a role in obstruction of trabecular meshwork.24 Other hypotheses are an inhibition of the phagocytosis of foreign matter by trabecular endothelial cells25 and decreased synthesis of prostaglandins that regulate aqueous humor outflow.26 Southern27,28 and Weinstein et al29 found abnormal glucocorticoid metabolism in trabecular tissue from patients with primary open-angle glaucoma (POAG). This finding may explain the increased susceptibility of patients with POAG to the ocular hypertensive effects of glucocorticoids. Alternatively, if steroids cause changes that would tend to result in a reduced outflow facility in most or all human eyes, those individuals with marginal or compromised outflow facility to begin with, would be expected to show the greatest rise in IOP.

Cultured human trabecular meshwork cells secrete increased amounts of laminin and integrin when exposed to dexamethasone, and similar mechanism may be operative in vivo.30 Other changes include thickening of the trabecular beams, alteration in F-actin architecture, increased cross-linked actin and induction of myocilin protein,31,32 which may have a role in trabecular obstruction in vivo. It has been reported that histochemical studies of trabeculectomy specimens when stained with Alcian blue, PAS and colloidal iron in steroid-induced glaucoma contained acid mucopolysaccharides in the outflow channels. It is suggested that corticosteroids cause rise of intraocular pressure acting through acid mucopolysaccharides but the exact mechanism is not known. In doubtful cases, as to the cause of glaucoma, demonstration of acid mucopolysaccharides in trabeculectomy specimens has weighed in favor of steroid-induced glaucoma.33 In animal study done by Shinzato et al, short-term application of steroids-induced downregulation of type I collagen C-propeptides. This could reflect impaired collagen turnover in the TM of glucocorticoid-treated eyes.34

RISK FACTORS

Certain groups were found to have higher rates of steroid responsiveness, including persons with diagnosed primary open-angle glaucoma (POAG).35 Approximately, one-third of glaucoma suspects and more than 90% of POAG patients responded with an IOP elevation greater than 6 mm Hg after receiving a 4-week course of topical dexamethasone 0.1%.36,37 First-degree relatives of POAG patients increased one’s susceptibility to being a steroid-responder.38,39 IOP elevations are more prominent in older adults compared with younger adults.38

However, children are also at risk for an increased IOP in response to steroids. Lam et al found that 71 and 59% of children receiving topical dexamethasone 0.1% (qid and bid respectively) had a subsequent IOP measurement greater than 21 mm Hg.40 Of those children receiving dexamethasone qid or bid, 36 and
21% respectively had an IOP greater than 30 mm Hg. Age, as a risk factor, appears to occur in a bimodal distribution peaking first at age of 6 years. As one progresses through adulthood, the risk rises again in late adulthood. Diabetes, high myopia and connective tissue disease are the other associations.

Genetics: Upregulation of myocilin gene by dexamethasone led many investigators to believe that myocilin gene induction may be involved in steroid-induced glaucoma. However, a putative association between MYOC induction and OAG has not been firmly established.

EPIDEMIOLOGY
Armany et al indicated that approximately one-third of normal eyes and more than 90% of patients with primary open-angle glaucoma respond with greater than 6 mm Hg of IOP elevation after receiving a 4-week course of topical dexamethasone 0.1%. Although, the most reported cases of corticosteroid-induced glaucoma are transient and managed with topical medications, progressive optic nerve damage has been reported but not demonstrated by visual field defects.

NATURAL COURSE
Steroid-induced damage of optic nerve is nonprogressive and further progression cessates with discontinuation of steroids. Esplidora et al studied patients with cortisone-induced glaucoma and reported that patients, who had instilled the medication for less than 8 weeks recovered normal ocular pressure after discontinuation of the corticoid. On the contrary, those who had employed the corticoid for more than 4 years did not regain normal ocular tension, and medical treatment or even surgical therapy in a large number of cases had to be employed. Thus, a prolonged use of steroids seems to lead to greater ocular damage. In a study by Sihota et al, all patients could be taken off treatment at 18 months. The duration of steroid use does not determine the IOP rise. Godel et al noted that the duration of treatment with systemic steroids was not associated with the rise in IOP. Acute rise of IOP within hours has been reported in open-angle glaucoma cases with the use of intensive steroid therapy and with the topical use of potent steroids.

PREVENTION
Low potency steroids like fluoromethalone were postulated as non-IOP raising steroids, but caution is needed as they have been reported to cause IOP spike in susceptible individuals. Studies done with steroids like loteprednol etabonate, which rapidly degrades into an inactive metabolite have not shown rise of IOP even in steroid responders.

TREATMENT
Cessation of steroid therapy at the earliest is the first line of defense and often all that is required. Chronic form abates in 1 to 4 weeks and acute form resolves in hours. Glaucoma may persist in spite of stopping steroids in some cases. In study by Francois et al glaucoma persisted in 2.8% of patients and they had a family history of glaucoma. Duration of steroid therapy also influences reversibility of IOP elevation. Esplidora et al reported normalizing of IOP in cases where steroids were used for less than 2 months and chronic elevation of IOP in cases where it was used for more than 4 years. Antiglaucoma drugs have to be instituted depending on the baseline IOP. Prostaglandin analogs, alpha agonists, beta-blockers can be prescribed alone or in combination depending on baseline IOP. Scherer et al have reported a 28% decrease in IOP with latanoprost in eyes having steroid-induced glaucoma. Prostaglandin analogs have been found to increase redness in eyes with VKC. Younger age of onset, high baseline IOP and greater glaucomatous optic neuropathy are more likely to need surgery. A study of juvenile glaucomas found that four of 11 steroid glaucoma eyes (36.6%) required surgery. In a study by Honjo et al success rate was of 83% in 5 years for trabeculectomy in the cases of steroid-induced glaucoma. Alternate treatment for exacerbation of VKC is needed in patients not responding to conventional drugs like mast cell stabilizers and antihistaminics. Topical cyclosporin drops in a concentration of 2% are used as steroid sparing agents in VKC. Recent studies have found similar efficacy of low dose cyclosporin in a concentration of 1 and 0.05%. Present authors have not found any detrimental effects on bleb with concurrent use of cyclosporin 2% instituted early after trabeculectomy in their unpublished three consecutive cases of steroid glaucoma having undergone trabeculectomy.

REFERENCES