Review Article

Steroid Induced Glaucoma: Dilemma Decoded

Shweta Tripathi[1], Shalini Mohan[2], Jatinder Singh Bhalla[3], Kanika Jain[3], Ashwini Kulkarni[3]

[1]Department of Ophthalmology, Indira Gandhi Eye Hospital and Research Centre, Lucknow, Uttar Pradesh, India.
[2]Department of Ophthalmology, Ganesh Shankar Vidyarthi Memorial (GSVM) Medical College, Kanpur, Uttar Pradesh, India.
[3]Department of Ophthalmology, Delhi Govt Deen Dayal Upadhyay Hospital (DDU) Hospital, New Delhi, India.

Abstract *Topical and systemic steroids are used to treat many clinical conditions but its use is not without side effects. Amongst the ocular side effects cataract and glaucoma are prominent. With the rising magnitude of glaucoma, it has become imperative to understand the pathophysiology, risk factors and management of Steroid Induced Glaucoma. This review attempts to decode the dilemma.*

Delhi J Ophthalmol 2022; 32; 15-19; Doi http://dx.doi.org/10.7869/djo.735

Keywords: *Steroid, Glaucoma, IOP*

Introduction

Corticosteroids are anti-inflammatory drugs commonly implicated in treatment of various ocular and systemic conditions. Steroids are known to induce ocular hypertension when administered by routes such as topical, periocular, systemic or inhalational routes.[1]

McLean[2] reported a rise in IOP induced by systemic administration of adrenocorticotrophic hormone (ACTH). After 4 years, Francois[3] described the first case of elevated IOP induced by local administration of steroid (cortisone). In 1963, Becker and Mills[4] demonstrated that patients who had glaucoma, or had been diagnosed as glaucoma suspects, had marked IOP rises in response to several weeks' exposure to topical corticosteroid.

Individuals who develop an increase in IOP following steroid use are referred to as "**steroid responders**".

Steroid responsiveness has been defined as follows over time

1) IOP increase > 5 mm Hg;
2) IOP above 21 mmHg;
3) IOP increase > 5 mm Hg with values above 24 mm Hg;
4) IOP increase > 10 mm Hg over baseline with clinical significance, the last being the most widely accepted definition.[29]

Armaly and Becker suggested three categories: for steroid responders [4-8]

1. High responders (4 to 6% of the population) – developed an IOP greater than 31 mm Hg or a rise of more than 15 mm Hg from baseline.
2. Moderate responders (about 1/3 of the population)- developed an IOP between 25-31 mm Hg or a rise of 6-15 mm Hg from baseline.
3. Non-responders (about 2/3 of the population) – found to have an IOP less than 20 mm Hg or a rise of less than 6 mm Hg from baseline.

Risk Factors

The important risk factors for steroid induced glaucoma are listed in (Table 1).

1. **Susceptibility:** Individual differences in the risk of steroid-induced IOP elevations are present. One possible explanation is the different expression of the 2 GR isoforms, GRa and GRb, GRb levels were found to be lower in TM cells isolated from glaucomatous eyes.[29]
2. **Age:** Older patients demonstrated higher risk of IOP elevation development after administration of GC eye drops. In children, the IOP elevation and possible resultant glaucomatous damage can have an earlier onset, be more severe at presentation, and progress more rapidly compared to adults.[29] IOP spike was most commonly seen in children on topical steroid therapy for vernal keratoconjunctivitis. In a case series conducted in Singapore, forty-one of 145 (28.3%) patients with severe VKC developed a corticosteroid response, of which eight (5.5%) progressed to glaucoma.[30]
3. **Glaucoma diagnosis:** An elevation in IOP in response to corticosteroid therapy is more frequently observed in patients with POAG.
4. **Others:** Connective tissue disease, high myopia, type I diabetes mellitus and angle-recession glaucoma.

Table 1: Risk factors for steroid induced glaucoma

S.No.	Risk Factor
1	Increasing age
2	Glaucoma suspects
3	Connective tissue disease[9]
4	High myopia[13-14]
5	Type I diabetes[10]
6	First-degree relative with primary open-angle glaucoma (POAG)[5,11-12]
7	Angle recession glaucoma

Pathogenesis

Steroid-induced glaucoma is open angle glaucoma with suggested mechanisms (Figure 1) for IOP elevation as follows:

- Steroid causes stabilization of lysosomal membranes and accumulation of polymerized glycosaminoglycans (GAGs) in the trabecular meshwork which produce biological edema leading to increased outflow resistance.[15-17]
- Glucocorticoids also increases the expression of extracellular matrix protein (fibronectin, GAGs, elastin, and laminin) within the trabecular meshwork cells which leads to increased trabecular meshwork resistance.[18-19]

- Corticosteroids cause inhibition of phagocytotic properties of endothelial cells lining the trabecular meshwork which leads to accumulation of aqueous debris.[20]
- Glucocorticoids have been shown to alter the trabecular meshwork cell morphology by causing an increase in nuclear size and DNA content.[21]
- FKBP06–binding immunophilin FKBP51 mediates nuclear transport of the human glucocorticoid receptor beta, which may play a role in increased glucocorticoid responsiveness.[22]
- Glucocorticoid decreases the synthesis of prostaglandin, which regulates the aqueous outflow.[23]
- Several genes have been found to be associated with both protective and damaging glucocorticoid-treated trabecular meshwork cells.[23]
- Myocilin (MYOC) is a gene identified as being induced by GC in the TM, other genes induced by GC in the TM include serine protease inhibitor (alpha1-antichymotrypsin), pigment epithelium-derived factor (PEDF), cornea-derived transcript 6, prostaglandin D-2 synthase, secretory leukocyte protease inhibitor (SLP1), serum amyloid A2 (SAA2), angiopoietin-like 7 protein (ANGPTL7), serum amyloid A1 (SAA1), serpin peptidase inhibitor, clade A3 (SERPINA3), zinc finger and BTB domain containing 16 protein (ZBTB16), and growth arrest specific protein 1 (GAS1).[29]

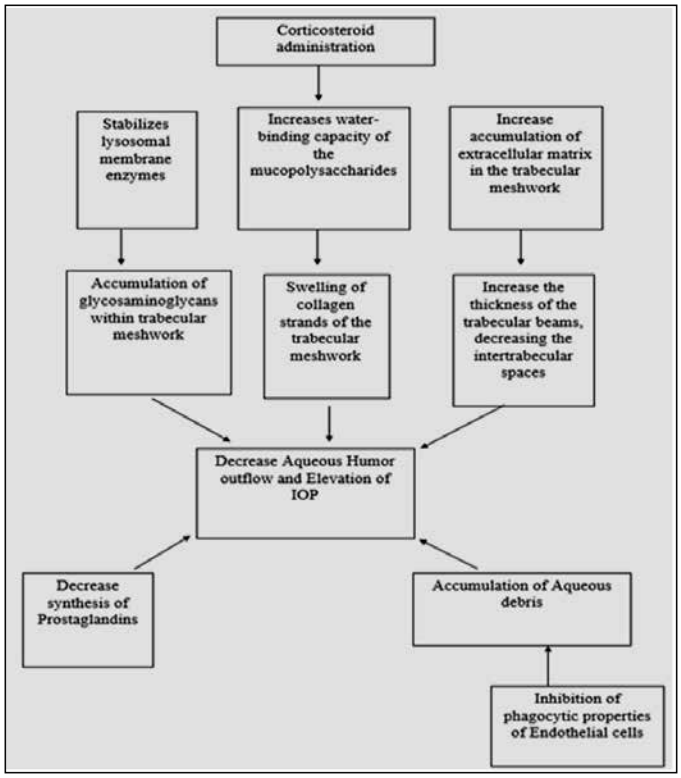

Figure 1: *Various mechanisms of steroid induced glaucoma*

Clinical Features

The clinical features of corticosteroid induced glaucoma are similar to those of POAG, with associated history of steroid usage.

The persistent elevated IOP increases the risk of optic nerve damage, leading to characteristic visual field changes similar to that with POAG.

Other associated ocular findings are Posterior subcapsular cataract, red eye (Due to Uveitis /Vernal keratoconjunctivitis for which the patient was on steroid therapy).

Routes of Steroid Administration

IOP elevation is caused by exogenous administration more than endogenous administration.

Topical therapy: IOP rise after steroid therapy occurs more frequently with topical administration as seen with eye drops or ointments (Table 2).

Periocular therapy: Prolonged duration of action in subconjunctival, subtenon, or retrobulbar injection of steroids is responsible for profound IOP spike.

Intravitreal therapy : (Table 3**)** IOP rise with intravitreal depot steroid has been seen in a large percentage of patients. Ozurdex is a slow-release intravitreal implant of dexamethasone used in the treatment of macular edema secondary to vein occlusions and for the treatment of uveitis. Dexamethasone-induced ocular hypertension is transient and is >10mmHg in 12.6% of patients. Dexamethasone is a more water-soluble steroid than triamcinolone or fluocinolone acetonide, IOP spike is better controlled without causing any ocular complications.45 Intravitreal injection of triamcinolone can increase IOP by several mm Hg in about 50% of patients, within 2 to 4 weeks after the start of treatment.[1]

Potency of Steroids

IOP elevation or glaucoma can occur as a consequence of exogenous GC administration through the topical, intraocular, periocular, oral, intravenous, inhaled, nasal, and transcutaneous routes(Table 2 , 3 and 4).[29]

Evaluation

- Visual acuity (VA) is likely to be normal except in advanced cases.
- Tonometry prior to pachymetry, noting the time of day.
- Gonioscopy: It is key to diagnosis as it allows the clinician to assess the status of the anterior segment angle, as Steroid induced glaucoma is a secondary OAG.
- Optic disc examination for glaucomatous changes (see below) should be performed with the pupils dilated, provided gonioscopy does not show critically narrow angles. Red-free light can be used to detect RNFL defects.
- Perimetry: to evaluate visual field changes in long standing cases.

Differential Diagnosis

- Primary open angle glaucoma
- Normal tension glaucoma
- Juvenile open angle glaucoma
- Uveitic glaucoma
- Glaucomatocyclitic crisis

Table 2: IOP changes in topically administered glucocorticoids[29]

Glucocorticoids	Range of IOP increase (mmHg)	Duration of administration (weeks)	Dose Regimen	Proportion of patients in whom hypertension developed (%)
Dexamethasone	9-22	3-12	QID	45.8
Betamethasone	5-16	4-6	QID	13
Prednisolone	9-22	2.5-12	QID	44
Difluprednate	>10- >21	>10 >21	BD QID	3
Loteprednol etabonate	<10- >10	1-6 4-96	QID BD	0.8-16
Fluorometholone	2.9-6	5-6	QID	0-88.3
Rimexolone	6.2- >10	5.2-6	QID	30
Clobetasone butyrate	1.2-4	6	TDS, QID	-

Table 3: IOP changes in intra-vitreally administered glucocorticoids[29]

Route of administration	Glucocorticoids	Range of IOP increase (mm Hg)	Onset of hypertension (weeks)	Duration of administration (months)	Proportion of patients in whom hypertension developed (%)
IVT injections	Dexamethasone (0.8 mg)	>21	1 day	1	45.8
	Triamcinolone acetonide (4 mg)	>21 >24	1-20	1-12	44
IVT implants	Fluocinolone acetonide (0.59 mg; 2.1 mg; 0.2 mg/d)	>10 <30 <40	2-4	9-12	0-88.3
	Dexamethasone (0.7 mg)	>10 >25 >35	1-12	2-12	0.8-16

Table 4: IOP changes in systemically administered glucocorticoids[29]

Route of administration	Extent of IOP increase (mmHg)	Period of administration (weeks)	Dose regimen	Proportion of patients in whom hypertension developed (%)
Oral route	24-32	<1-11 months	-	4.9
Intravenous route	0.8-1.6	1 day	3	
Percutaneous route	32-39.4	2-5 years	-	77.4
Inhalation route nasal route	22-37	1-4 months	12-72	3-4.33

Management

"Prevention is the cure" when it comes to steroid induced glaucoma.

- Discontinuation of the use of the steroid is the first line of management, acute rise of IOP normalizes within days and chronic forms take 1 to 4 weeks after drug discontinuation.
- If IOP remains elevated anti-glaucoma medications or surgery may become necessary.
- The duration of steroid therapy also appears to influence the reversibility of the IOP elevation.[25]
- If possible, the use of steroids can be avoided in patients with pre-existing glaucoma as these are the individuals who are prone to steroid-responsiveness and may progress to significant visual loss i.e., End stage of the disease.
- When steroid therapy is unavoidable, the choice of drug should be of one that has a therapeutic effect at the lowest possible dose, administered by the safest route, minimizing the risk of all potential adverse effects. The corticosteroid response may take days to weeks to resolve within a few days of cessation of therapy.
- Alternative corticosteroid formulations for topical treatments can be chosen such as Fluoromethalone 0.1% which is claimed to have less effect on IOP.[23]
  For certain conditions nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used.
- For patients who need systemic corticosteroids, can be shifted to steroid sparing agents after consultation with Physician.

Follow Up for Patients on Steroid Therapy

A baseline measurement of IOP should be taken prior to Initiation of corticosteroid therapy. Patients on topical therapy should then have their IOP measured again 1-2

weeks after initiation of treatment, then every 4 weeks for 2–3 months, then 6-monthly if therapy is to continue.

Patients undergoing intravitreal triamcinolone should be monitored for several months following the steroid injection, as various studies have reported a rise in IOP even after 100 days of treatment.[24]

Ideally, patients requiring long-term systemic corticosteroid therapy should have glaucoma screening along with baseline documentation of all parameters and should have their IOP checked at 1, 3, and then every 6 months till the treatment is continued.

Treatment

The treatment of steroid induced glaucoma is same as of Primary Open Angle Glaucoma.

Medical Management

- After cessation of steroid therapy, Beta Blockers are first-line choice of drug for the condition.
- Prostaglandin Analogues are avoided in uveitic glaucomatous eyes.
- Carbonic anhydrase inhibitors &alpha agonist can be used as a 2nd /3rd line of drug.
- Rho kinase inhibitors can also be added if the response is poor to other anti-glaucoma medications.

Argon Laser Trabeculoplasty

This treatment has been tried both before and after commencing corticosteroid therapy and has not been shown to be effective in preventing corticosteroid induced pressure rises.[26-27]

Filtration Surgery

Trabeculectomy stays the most efficient surgical treatment of choice for cases who have persistently high IOP despite cessation of steroids and on maximum
medical therapy.

Excision of depot periocular or intraocular steroid may be explanted in some patients.[28]

Patient Education and Advice to Ophthalmologists

It is of utmost importance to advise patients against unsupervised usage of over-the-counter steroids for slight ocular discomfort and rather should seek consultation from a certified ophthalmologist.

Ophthalmologists especially the residents should be taught to use corticosteroids judiciously with appropriate tapering of the drug. Importance of regular IOP monitoring during corticosteroid regimen administered for various ocular and systemic diseases should be emphasized.

Conclusion

Steroid-induced glaucoma is a preventable iatrogenic disease. The rampant and irrational use of steroids by local medical practitioners, unmonitored use by patients themselves with over-the-counter steroids adds to the burden of the disease. It is important to identify those patients with risk factors (like POAG, family history, diabetes mellitus, connective tissue disorder, high myopia) along with detection of early stage of corticosteroid induced high IOP to prevent them from developing permanent visual loss. In most cases, corticosteroid-induced glaucoma can be treated successfully by topical antiglaucoma therapy along with cessation of corticosteroid therapy.

References

1. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. J Curr Glaucoma Pract 2017;11(2):67-72. doi: 10.5005/jp-journals-l0028-1226. Epub 2017 Aug 5. PMID: 28924342; PMCID: PMC5577123.
2. McLean JM. Use of ACTH and cortisone. Trans Am Ophthalmol Soc 1950; 48: 293–296.
3. Francois J. Cortisone et tension oculaire. Ann D'Oculist 1954; 187: 805.
4. Becker B, Mills DW. Corticosteroids and intraocular pressure. Arch Ophthalmol 1963; 70: 500–507 doi: 10.1001/archopht.1963.00960050502012. PMID: 14078872.
5. Becker b. intraocular pressure response to topical corticosteroids. Invest Ophthalmol. 1965 Apr;4:198-205. PMID: 14283013.
6. Armaly mf. statistical attributes of the steroid hypertensive response in the clinically normal eye. i. the demonstration of three levels of response. Invest Ophthalmol. 1965 Apr;4:187-97. PMID: 14283012.
7. Armaly MF. The heritable nature of dexamethasone-induced ocular hypertension. Arch Ophthalmol. 1966 Jan;75(1):32-5. doi: 10.1001/archopht.1966.00970050034007. PMID: 5900502.
8. Armaly MF. Inheritance of dexamethasone hypertension and glaucoma. Arch Ophthalmol. 1967 Jun;77(6):747-51. doi: 10.1001/archopht.1967.00980020749006. PMID: 6026182.
9. Gaston H, Absolon MJ, Thurtle OA, Sattar MA. Steroid responsiveness in connective tissue diseases. Br J Ophthalmol. 1983 Jul;67(7):487-90. doi: 10.1136/bjo.67.7.487. PMID: 6860617; PMCID: PMC1040100.
10. Becker B. Diabetes mellitus and primary open-angle glaucoma. The XXVII Edward Jackson Memorial Lecture. Am J Ophthalmol. 1971 Jan;71(1 Pt 1):1-16. doi: 10.1016/0002-9394(71)91088-9. PMID: 5099936.
11. Becker b, hahn ka. topical corticosteroids and heredity in primary open-angle glaucoma. Am J Ophthalmol. 1964 Apr;57:543-51. doi: 10.1016/0002-9394(64)92500-0. PMID: 14139296.
12. Davies TG. Tonographic survey of the close relatives of patients with chronic simple glaucoma. Br J Ophthalmol. 1968 Jan;52(1):32-9. doi: 10.1136/bjo.52.1.32. PMID: 5635901; PMCID: PMC506519.
13. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. Am J Ophthalmol. 1966 Dec;62(6):1038-43. PMID: 5957877.
14. Spaeth GL. Traumatic hyphema, angle recession, dexamethasone hypertension, and glaucoma. Arch Ophthalmol. 1967 Dec;78(6):714-21. doi: 10.1001/archopht.1967.00980030716005. PMID: 6064921.
15. Francois J. Tissue culture of ocular fibroblast. Ann Ophthalmol 1975 Dec;7(12):1551-1554.
16. Francois J. The importance of the mucopolysaccharides in intraocular pressure regulation. Invest Ophthalmol. 1975 Mar;14(3):173-6. PMID: 123231.
17. François F, Victoria-Troncoso V. Mukopolysaccharide und Pathogenese kortisonbedingter Augendrucksteigerung [Mucopolysaccharides and pathogenesis of cortisone glaucoma (author's transl)]. Klin Monbl Augenheilkd. 1974 Jul;165(1):5-10. German. PMID: 4277884.
18. Johnson DH, Bradley JM, Acott TS. The effect of dexamethasone on glycosaminoglycans of human trabecular meshwork in perfusion organ culture. Invest Ophthalmol Vis Sci. 1990 Dec;31(12):2568-71. PMID: 2125032.

19. Steely HT, Browder SL, Julian MB, Miggans ST, Wilson KL, Clark AF. The effects of dexamethasone on fibronectin expression in cultured human trabecular meshwork cells. Invest Ophthalmol Vis Sci. 1992 Jun;33(7):2242-50. PMID: 1607235.
20. Bill A. Editorial: The drainage of aqueous humor. Invest Ophthalmol. 1975 Jan;14(1):1-3. PMID: 1110131.
21. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. Prog Retin Eye Res. 1999 Sep;18(5):629-67. doi: 10.1016/s1350-9462(98)00035-4. PMID: 10438153.
22. Zhang X, Clark AF, Yorio T. FK506-binding protein 51 regulates nuclear transport of the glucocorticoid receptor beta and glucocorticoid responsiveness. Invest Ophthalmol Vis Sci. 2008 Mar;49(3):1037-47. doi: 10.1167/iovs.07-1279. PMID: 18326728; PMCID: PMC2442563.
23. Shepard AR, Jacobson N, Fingert JH, Stone EM, Sheffield VC, Clark AF. Delayed secondary glucocorticoid responsiveness of MYOC in human trabecular meshwork cells. Invest Ophthalmol Vis Sci. 2001 Dec;42(13):3173-81. PMID: 11726619
23. Shokoohi-Rad S, Daneshvar R, Jafarian-Shahri M, Rajaee P. Comparison between Betamethasone, Fluorometholone and Loteprednol Etabonate on intraocular pressure in patients after keratorefractive surgery. J Curr Ophthalmol. 2017 Dec 7;30(2):130-135. doi: 10.1016/j.joco.2017.11.008. PMID: 29988925; PMCID: PMC6033780.
24. Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD. Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. Ophthalmology. 2009 Mar;116(3):455-60. doi: 10.1016/j.ophtha.2008.10.002. Epub 2009 Jan 20. PMID: 19157561.
25. Espildora J, Vicuna P, Diaz E. Glaucome cortisonique. A propos de 44 yeux [Cortisone-induced glaucoma: a report on 44 affected eyes (author's transl)]. J Fr Ophtalmol. 1981;4(6-7):503-8. French. PMID: 7299067
26. Galin MA, Hirschman H, Gould H, Hofmann I. Does laser trabeculoplasty prevent steroid glaucoma? Ophthalmic Surg Lasers. 2000 Mar-Apr;31(2):107-10. PMID: 10743920.
27. Feroze KB, Khazaeni L. Steroid Induced Glaucoma. 2021 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28613653.
28. Kersey, J., Broadway, D. Corticosteroid-induced glaucoma: a review of the literature. Eye 20, 407–416 (2006). https://doi.org/10.1038/sj.eye.6701895
29. Roberti G, Oddone F, Agnifili L, Katsanos A, Michelessi M, Mastropasqua L, Quaranta L, Riva I, Tanga L, Manni G. Steroid-induced glaucoma: Epidemiology, pathophysiology, and clinical management. Surv ophthalmol. 2020 Jul 1;65(4):458-72. https://doi.org/10.1016/j.survophthal.2020.01.002
30. Ang M, Ti SE, Loh R, et al. Steroid-induced ocular hypertension in Asian children with severe vernal keratoconjunctivitis. Clin Ophthalmol. 2012;6:1253–1258. PMID: 22927736

Cite This Article as: Ashwini Kulkarni, Shweta Tripathi, Jatinder Singh Bhalla, Kanika Jain, Shalini Mohan. Steroid induced Glaucoma: Dilemma Decoded. Delhi J Ophthalmol 2022; 32 (3): 15 - 19.

Acknowledgments: Nil.

Conflict of interest: None declared

Source of Funding: None

Date of Submission: 26 Feb 2022
Date of Acceptance: 21 Mar 2022

Address for correspondence

Jatinder Singh Bhalla
MBBS,MS,DNB,MNAMS
Consultant Head of Glaucoma Services and Incharge Academics, Deen Dayal Upadhyay Hospital Hospital New Delhi, India.
E-mail: jsb_21@yahoo.com

Quick Response Code