

# Clinical Analysis of Steroids Induced Glaucoma: A Systematic Review

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## ABSTRACT

For more than 50 years, the elevation in intraocular pressure that can impede the administration of topical or systemic corticosteroids has been recognized. There has been increasing attention in this steroid-responsive phenomena since the identification of the myocilin gene (formerly known as the trabecular meshwork inducible glucocorticoid response or TIGR gene). In addition, the increasingly popular use of injectable intraocular steroids to treat clinically substantial subretinal fluid and macular oedema has increased the incidence. Animal studies, cell biology, molecular biology, and a better grasp of genetics have all contributed to a better understanding of the response's mechanics. The electronic MEDLINE, Embase, Cochrane, and PubMed databases were searched. Additionally, the bibliography of all relevant articles and textbooks were manually searched. To determine the link between plasma cortisol levels and steroid-induced glaucoma, plasma cortisol levels can be tested once every four hours. It can also be done on a bigger group of people. The steroid provocative test will aid in the identification of individuals who are high steroid responders in the general population. It can also be used in patients who require intravitreal triamcinolone injections. Genetic research could shed further light on the aetiology of steroid-induced glaucoma.

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## INTRODUCTION

Steroid-induced ocular hypertension is an increase in intraocular pressure (IOP) caused by the usage of glucocorticoids (GCs) in the eye. Glaucomatous optic neuropathy can develop if the IOP rises to a certain level and is not addressed. Steroid-induced glaucoma is the name given to this condition (SIG).

“Steroid responders” are people who have an increase in their IOP after taking GC. Several definitions of steroid responsiveness have been presented over the years: 1) An increase in IOP of more than 5 mm Hg; 2) An increase in IOP of more than 21 or 24 mm Hg; 3) An increase in IOP of more than 5 mm Hg with values greater than 24 mm Hg; and 4) An increase in IOP of more than 10 mm Hg over baseline with clinical significance, the latter being the most widely accepted definition.<sup>1,2</sup>

As a side effect of corticosteroid medication, an increase in intraocular pressure (IOP) can develop. Damage to the optic nerve (steroid-induced glaucoma) can occur if the ocular hypertensive effect is large enough and lasts long enough. McLean<sup>3</sup> reported an increase in IOP caused by systemic adrenocorticotropic hormone injection in 1950. (ACTH). Francois<sup>4</sup> documented the first case of increased IOP caused by local steroid treatment after 4 years (cortisone). Since then, researchers have continued to be interested in this sort of secondary ocular hypertension/glaucoma, both for its own sake and to learn more about the aetiology of certain types of open-angle glaucoma (OAG).

IOP has long been known to fluctuate during the day, and it has been suggested that this is linked to cortisol levels.<sup>5</sup> The daily variability in IOP correlates closely with plasma cortisol levels, with the peak occurring about 0700 hours and the trough occurring in the early evening. Furthermore, cases of elevated IOP due to adrenal gland hyperplasia<sup>6,7</sup> have been reported, and while clear cause and effect has yet to be shown, it is known that patients who have had their adrenals removed have no diurnal IOP variation.<sup>5</sup>

Steroid-induced glaucoma is a type of secondary open-angle glaucoma that is most often caused by topical corticosteroids, but can also be caused by systemic corticosteroids. Although there are numerous

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articles on steroid responsiveness,<sup>8,9</sup> no prospective research of steroid-induced glaucoma has been done to our knowledge. Anecdotal evidence of the natural history of steroid-induced glaucoma and the behavior of intraocular pressure (IOP) after stopping corticosteroids has been gathered.

The goal of this systematic review is to summarize the risk factors for developing corticosteroid-induced glaucoma, including the effect of preparation type, examine the underlying mechanisms and genetics of the disease, and give therapy alternatives.

## AIM AND OBJECTIVES

### Aim

To evaluate the clinical analysis of steroid induced glaucoma.

### Objectives

To assess:

1. The risk factors for developing corticosteroid-induced glaucoma
2. Examine the underlying mechanisms and genetics of the disease,
3. Give therapy alternatives.

## METHODS

### PROTOCOL AND REGISTRATION

The present systematic review was registered at the National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews.

Registration number: \_\_\_\_\_

The search protocol is designed based on the PRISMA (Preferred reporting Items for systematic Reviews and meta-analysis) guidelines 2009.

### SEARCH STRATEGY

The electronic MEDLINE, Embase, Cochrane, and PubMed databases were searched. Additionally, the bibliography of all relevant articles and textbooks were manually searched. Based on the inclusion and exclusion criteria, 2 reviewers ) independently selected the relevant articles. Any disagreement was discussed between the 2 reviewers until a consensus was reached.

Using the PICO-formatted question, methodological Medical Subject Heading (MeSH) terms were generated to make the search strategy more sensitive in the identification of studies. These terms included (“Glucocorticosteroids” [MeSH] AND (“Glaucoma” [MeSH]) AND (“Clinical analysis” [MeSH]. Studies that met these inclusion criteria underwent critical analysis. The qualities of the included studies were evaluated according to a proposed specific quality assessment scale.

### Inclusion Criteria

The following types of studies were considered:

1. Studies regarding steroids induced glaucoma published in English language peer reviewed scientific journals from 2009 to 2021.

2. Studies in which the outcome was defined
3. All the articles published till December 2021 were included
4. Full articles in English were included.

### Exclusion Criteria

The exclusion criteria included the following:

1. case reports, case series,
  2. cross-sectional studies,
  3. laboratory studies (cadaver),
  4. or animal studies,
  5. Reviews
  6. Abstracts,
  7. Articles with incomplete data and patients with presence of any lesions were excluded.
  8. Articles in any other language except English.
- The references of selected articles were also analysed for additional studies. and any study that did not meet the inclusion criteria.

### Formulating the Review Question

The research question was set in accordance with the PICO format (Population, Intervention, Comparison, and Outcome).

The following PICO framework was developed for a systematic review of the existing literature regarding the risk factors for developing corticosteroid-induced glaucoma, including the effect of preparation type, examine the underlying mechanism and genetics of the disease, and give therapy alternatives.

### Selection

The study selection was done in a three step process All the titles were reviewed and based on the inclusion and exclusion criteria, appropriate studies were selected. For all the selected titles, abstracts were obtained and reviewed, from which appropriate abstracts were selected based on the criteria. For all the selected abstracts, full text articles were obtained and analyzed, and the final set of articles were obtained keeping in mind the selection criteria (Table 1).

Finally 9 articles were selected for the study.

### Data Extraction

Data extraction was done using the data extraction forms. The following parameters were extracted: authors, year of study, study design, number of patients, gender, mean age, intervention data about the steroids induced glaucoma in patients. If patients were followed up, duration of follow up and presence or absence of recurrence was recorded for all the articles.

**Table 1:** Selection of studies based on inclusion and exclusion criteria

|                             |     |
|-----------------------------|-----|
| Initial search              | 110 |
| Duplicates and non relevant | 41  |
| Case reports and series     | 13  |
| Reviews                     | 29  |
| Abstract                    | 14  |
| Language other than English | 8   |

### Quality Assessment

Quality assessment for the studies was performed using the Cochrane collaboration tool for assessing risk of bias in RCTs. The Cochrane Collaboration’s tool for assessing risk of bias, the Oxford Systematic Review Appraisal Sheet, Critical Appraisal Skills Programme, Newcastle- Ottawa Quality Assessment Form for Cohort Studies, and the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading evidence were used to ensure the accuracy of this data analysis in this systematic review.<sup>10-13</sup> The following were assessed: Selection bias which included random sequence generation and allocation concealment, performance bias, attrition bias, reporting bias and any other bias observed. High, low and unclear risk was assigned for each bias. Three observers assessed independently and any disagreement was settled by discussion.

The protocol for this systematic review was developed following established guidelines<sup>10</sup> Also, a well-defined review question was developed by using the patient population, intervention, comparison, and outcome (PICO) framework.

### RESULTS

On initial search 110 articles were obtained. Out of a total of 110 articles of the database search, after removal of duplicates and elimination based on eligibility criteria, a total of 5 studies were included for analysis (Flow Chart).

#### Synthesis of Results

Narrative synthesis has been provided for the findings obtained from the studies. The data extracted has been presented in the tabular form. (Table 2).

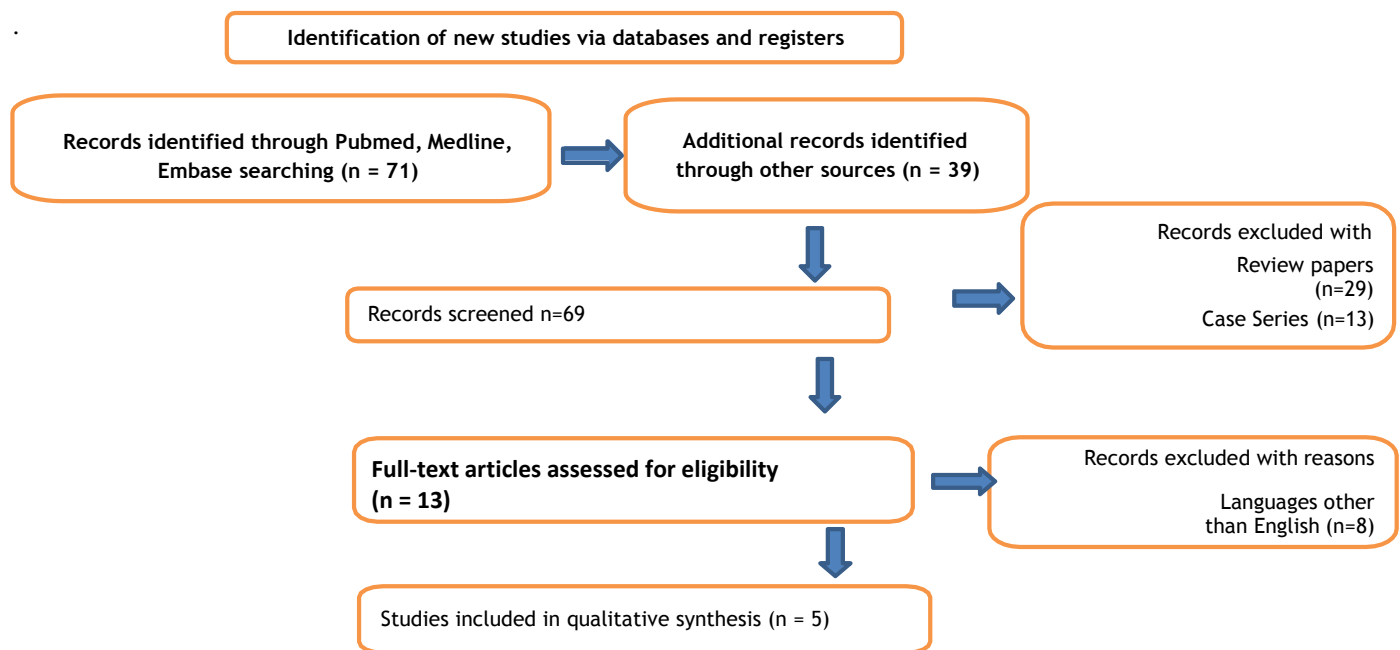


Figure: PRISMA flow chart

**Table 2:** Intervention and outcomes of selected studies

| Study                                 | Population  | Intervention   | Outcome  |
|---------------------------------------|---|--|--|
| Mohan R et al (1989) <sup>14</sup>    | 2392 patients who attended glaucoma clinic  | Topical and systemic steroids                        | Among the corticosteroids, dexamethasone and betamethasone both topical and systemic are more potent in producing cataract and glaucoma than medrysone and prednisolone. |
| Sihota R (2008) <sup>15</sup> et al.  | 34 patients having steroid-induced glaucoma were prospectively evaluated after cessation of steroid for IOP | Steroid therapy                                      | Patients with steroid- induced glaucoma, who were r 20 years old, with a higher IOP, and greater glaucomatous optic neuropathy, were more likely to need surgery         |
| Gupta S (2015) <sup>16</sup> et al.   | 1259 cases of pediatric glaucoma presenting at center over 5 years  | Steroids   | Glaucomatous optic neuropathy was the cause of blindness in children.  |
| Ngai P (2016) <sup>17</sup> et al.    | A nonrandomized, non blinded, retrospective study of 20 subjects with steroid response was conducted        | Trabectome surgery on patients with steroid response | The Trabectome procedure is safe and highly effective for steroid-response glaucoma, even in the context of continued steroid treatment.                                 |
| Senthil S (2020) <sup>18</sup> et al. | 4062 vernal kerato conjunctivitis subjects visiting from 1992 to 2009                                       | Steroids therapy                                     | Disease predominantly affected adolescent males. Glaucoma was severe with one-third needing surgery and one-third blind due to SIG.                                      |

**Table 3:** Distribution of studies based on risk of Bias assessment

| Authors name                         | Selection Bias<br>Random<br>sequence<br>generation | Allocation<br>Concealment | Reporting bias | Others   | Performance<br>bias<br>Blinding<br>participants<br>and personnel | Blinding<br>Outcome | Attrition bias |
|--------------------------------------|--|---------------------------|----------------|----------|--|---------------------|----------------|
| Mohan R et al. (1989) <sup>14</sup>  | Low risk   | Low risk                  | Low risk       | Low risk | Low risk   | Unclear             | High risk      |
| Sihota R et al. (2008) <sup>15</sup> | Low risk   | Low risk                  | Low risk       | Low risk | Low risk   | Low risk            | Low risk       |
| Gupta S et al. (2015) <sup>16</sup>  | Low risk   | Low risk                  | Low risk       | Low risk | Low risk   | Low risk            | Low risk       |
| Ngai P et al (2016) <sup>17</sup>    | Low risk   | Unclear                   | Low risk       | Low risk | Low risk   | Unclear             | Low risk       |
| Senthil S et al (2020) <sup>18</sup> | Low risk   | Low risk                  | Low risk       | Low risk | Unclear  | Unclear             | Low risk       |

## Risk of Bias Assessment

Risk of bias was assessed using Cochrane Risk of Bias Assessment Tool. Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other). Risk of selection, reporting, and other bias are assessed in the Quality Assessment Form Part I. Risk of performance, detection, and attrition bias are assessed using the Quality Assessment Form Part II.

Using the guidance provided at the end of the form, risk of bias was selected as “high”, “low” or “unclear” for each judgment rises due to reduced trabecular outflow (Table 3).

When corticosteroids are used locally or systemically, IOP rises, but the reaction varies from person to person. IOP response normally takes 2 to 4 weeks after commencing topical steroids, while in rare cases, systemic steroid or adrenocorticotropic hormone use can cause an abrupt elevation in IOP within hours (ACTH). Steroid-induced glaucoma is a common consequence of vernal keratoconjunctivitis (VKC), as patients require long-term therapy and steroids are frequently administered to provide early alleviation of symptoms.

The widespread use of intravitreal triamcinolone acetonide (IVTA) for subretinal fluid, macular edema, and adjunctive therapy for choroidal neovascularization has resulted in an increase in corticosteroid-induced ocular hypertension and glaucoma. In our investigation, triamcinolone was administered intravitreally to two individuals. One is for diabetic retinopathy with macular edema, while the other is for macular edema caused by a clogged central retinal vein. Due to elevated IOP on presentation that could not be managed with medicine, both of them had trabeculectomy.<sup>19</sup>

Pre-existing POAG or having a first-degree relative with POAG are both significant risk factors for corticosteroid-induced glaucoma. Increased risk tends to occur in a bimodal distribution, peaking around age 6, and may be a risk factor. As one becomes older, age may become less of a role until late adulthood, when the risk increases again. Finally, patients with connective-tissue disease, type 1 diabetes, and extreme myopia should all be considered high-risk, and careful monitoring and follow-up is required throughout extended corticosteroid treatment.<sup>20</sup>

High-risk patients who receive intravitreal injections require examinations one day and one week after treatment and at least monthly follow-up examinations after the medication's cessation.<sup>21</sup>

## CONCLUSION

Steroids should be avoided or, if necessary, taken in lesser doses in vulnerable individuals and those with risk factors. Patients who had cataract surgery were more affected, according to our research, due to the continuing use of topical steroids. Once the eye is quiet, the topical steroid administration should be ceased. Alternatively, those who are prone to glaucoma after surgery should be provided nonsteroidal anti-inflammatory medicines. In these people, IOP should be assessed on a regular basis.

To determine the link between plasma cortisol levels and steroid-induced glaucoma, plasma cortisol levels can be tested once every four hours. It can also be done on a bigger group of people. The steroid provocative test will aid in the identification of individuals who are high steroid responders in the general population. It can also be used in patients who require intravitreal triamcinolone injections. Genetic research could shed further light on the aetiology of steroid-induced glaucoma.

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