Axial Length as a Risk Factor for Steroid-Induced Ocular Hypertension

Wungrak Choi, Jung Dong Kim, Hyoung Won Bae, Chan Yun Kim, Gong Je Seong, and Min Kim
Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, Korea.

Purpose: In this study, we aimed to assess whether axial length (AXL) is a true risk factor for steroid-induced ocular hypertension (OHT). We hypothesized that the proportion of patients with steroid-induced OHT among individuals who have received intravitreal dexamethasone (DEX) injections would differ according to the AXL of their eyes.

Materials and Methods: A single-center, cross-sectional, case-control study was conducted on 467 eyes that underwent DEX implant injection owing to various retinal diseases. Intraocular pressure (IOP) was measured before the injection and 1 week and 1, 2, 3, 6, and 12 months after the injection. Enrolled patients were divided into OHT and normal IOP groups. Univariable logistic regression analysis was used to calculate odds ratios of steroid-induced OHT with significant variables being analyzed using a multivariable model.

Results: A longer AXL was identified as a risk factor for steroid-induced OHT via both univariable and multivariable analyses, with an odds ratio of 1.216 [95% confidence interval (CI): 1.004–1.472, \( p=0.0452 \)]. The optimal cut-off value for AXL in terms of steroid-induced OHT was 23.585 mm, with an odds ratio of 2.355 (95% CI: 1.429–3.882, \( p=0.0008 \)).

Conclusion: Our findings indicate that a long AXL is a risk factor for steroid-induced OHT. Further, clinicians should be aware of steroid-induced OHT when treating patients with high myopia with steroids.

Key Words: Dexamethasone, intraocular pressure, myopia, axial length, ocular hypertension

INTRODUCTION

Although ophthalmologists commonly encounter patients with steroid-induced ocular hypertension (OHT), the risk factors for this condition remain unclear. As avoiding steroid usage among high-risk patients is an optimal way of preventing steroid-induced OHT, there is a clinical need to determine such risk factors. High myopia is one such possible risk factor; although evidence in support thereof is limited. To our knowledge, very few studies have been conducted to assess the association between axial length (AXL) and steroid-induced OHT.

The first study on myopia and steroid-induced OHT was conducted in 1966. Therein, 17 patients with high myopia received 0.1% dexamethasone (DEX) eye drops for 6 weeks. Patients with high myopia exhibited a higher risk of developing steroid-induced OHT than other patients. Accordingly, most ophthalmologists accept high myopia as a risk factor for steroid-induced OHT. However, that study had a small sample, and although high myopia was defined as a myopic refractive error >5.0, the exact AXL was not reported. These findings have not been confirmed in larger studies to date. In a recent study, a short AXL (<23.00 mm) was a risk factor for steroid-induced OHT. Given the need to confirm these findings, we conducted the present study to verify whether short and long AXLS are risk factors for steroid-induced OHT. We hypothesized that the occurrence of steroid-induced OHT among patients who have received intravitreal DEX injections would differ according to their AXL.
MATERIALS AND METHODS

Patient enrollment
This retrospective study was conducted on patients who underwent DEX implantation between March 2014 and May 2019 at Yonsei University Health System, Korea. The inclusion criteria were availability of AXL data and records of intraocular pressure (IOP) measurements up to 12 months post-injection. Information on the patients’ medical history, sex, primary diagnosis, age, and ocular examination was obtained from the medical records. Ocular assessments included measurements of IOP, AXL, and central corneal thickness and fundus examination.

This study was approved by the Institutional Review Board of Gangnam Severance Hospital. The requirement for informed consent was waived since this study was a retrospective review of existing medical records (IRB number: 3-2020-0310). The study protocol adhered to the tenets of the Declaration of Helsinki and was in compliance with the Health Insurance Portability and Accountability Act.

Study design
A total of 467 eyes were finally eligible for inclusion. Patients who underwent one DEX implantation were included in the study. We defined and classified IOP elevation as previously described: a post-injection IOP ≥25 mm Hg or an IOP elevation ≥10 mm Hg over the baseline measurement. The baseline measurement was defined as the initial IOP before DEX implantation. IOP was evaluated at seven time points: baseline IOP before injection and IOP 1 week and 1, 2, 3, 6, and 12 months after DEX implantation. The included patients were divided into an OHT and a normal IOP group.

Intravitreal DEX injections
Intravitreal injections were administered as previously described. Briefly, an eyelid speculum was used to stabilize the eyelids and each eye was sterilized and flushed with 5% povidone iodine eye drops before the injection. The injection was administered under topical anesthesia; 0.5% Alcaine (proparacaine hydrochloride) eye drops. The injections were administered 3.5 mm posterior to the corneal limbus through the pars plana, and a 0.7-mg DEX implant (Ozurdex; Allergan Inc., Irvine, CA, USA) was inserted.

IOP measurements
IOP measurements were performed as previously described. Briefly, patients underwent eye examinations before and after DEX implantation. IOP was measured using a non-contact tonometer (NCT; KT-800 tonometer; Kowa, Tokyo, Japan) or a Goldmann applanation tonometer (GAT). Unless there was a previous glaucoma diagnosis, the NCT was initially used to measure both pre- and post-injection IOP. However, in cases with a high IOP (>20 mm Hg), measurements were repeated using a GAT. The IOP measurements were obtained in triplicate within the same sitting, and the average value was considered the final IOP.

Statistical analysis
Data were analyzed with SPSS 22.0 software (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Institute, Cary, NC, USA), and R package version 3.4.4 (http://www.R-project.org). Continuous and categorical variables are expressed as the mean (SD) and number of patients (percentage), respectively.

Logistic regression analysis was used to calculate the odds ratio for steroid-induced OHT. The included variables were age, sex, AXL, central corneal thickness, glaucoma history [i.e., primary open-angle glaucoma (POAG), glaucoma suspect, neovascular glaucoma, angle-closure glaucoma, and secondary glaucoma], and medical history [i.e., connective tissue disease, thyroid disease, kidney disease, cancer, benign prostatic hyperplasia, tuberculosis, cardiovascular diseases, cerebrovascular accidents, hypertension, diabetes mellitus (DM), family history of glaucoma, previous history of uveitis, and penetrating keratoplasty]. Firth logistic regression was performed if zero observations in the group were recorded. After calculating odds ratios, significant variables were analyzed using a multivariable model. The optimal cut-off value of AXL for steroid-induced OHT was calculated using the Youden index. P values <0.05 indicated statistical significance.

RESULTS
The total proportion of steroid-induced OHT after DEX implantation was 16.9%. Table 1 summarizes the clinical characteristics of the normal and OHT groups. Major causes of macular edema requiring DEX implantation were diabetic macular edema (DME), retinal vein occlusion, and uveitis (Table 1).

The distribution of the highest postoperative IOP according to the AXL was analyzed via scatter plot analysis. The highest postoperative IOP was calculated for the AXL of each eye, and the trend line was analyzed (Fig. 1).

Univariable analyses for factors associated with steroid-induced OHT
Logistic regression analysis revealed that young age, male sex, long AXL, and absence of DM were significantly related to steroid-induced OHT development (p < 0.05) (Table 1).

Multivariable model results
Using all significant variables, we fitted a multivariable model to assess AXL as a risk factor for steroid-induced OHT. The odds ratio was 1.216 [95% confidence interval (CI): 1.004–1.472, p = 0.0452], which indicated that a long AXL is an independent risk factor for steroid-induced OHT (Table 2).
Distribution of steroid-induced OHT according to AXL
The patients were divided into six groups according to the AXL, from the shortest to the longest. Subsequently, the number and proportion of patients with steroid-induced OHT in each group was determined. The AXL of each group was as follows: <22 mm (group 1), 22 to <23 mm (group 2), 23 to <24 mm (group 3), 24 to <25 mm (group 4), 25 to <26 mm (group 5), and ≥26 mm (group 6). The proportion of patients with steroid-induced OHT in each group was as follows: 8.33% in group 1, 12.28% in group 2, 14.75% in group 3, 25.77% in group 4, 22.58% in group 5, and 27.27% in group 6. A continuous increase in the proportion of patients with steroid-induced OHT was observed as the AXL increased (Table 3A and B).

Optimal cut-off point of AXL for clinical use
The optimal cut-off value of AXL for steroid-induced OHT was 23.585 mm. Patients with an AXL ≥23.585 mm exhibited a higher risk of developing steroid-induced OHT than those with an AXL <23.585 mm, with an odds ratio of 2.355 (95% CI: 1.429–3.882, p=0.0008) (Table 3C and D).

DISCUSSION
Steroids are widely used to treat various ophthalmic diseases, and comitant steroid-related problems, including IOP, are common in the clinical field. Steroid-induced OHT can cause severe complications resulting from pressure-induced optic

Table 1. Clinical Characteristics and Results of Univariable Analyses of Factors that May Cause Steroid-Induced OHT (n=467)

| Variables                  | Normal (n=388) | OHT (n=79) | Univariable analyses OR (95% CI) | p value |
|----------------------------|----------------|------------|----------------------------------|---------|
| Age (yr)                   | 62.116±13.065  | 58.304±15.393 | 0.981 (0.964–0.997)               | 0.0239  |
| AXL (mm)                   | 23.568±1.201   | 24.000±1.259  | 1.304 (1.084–1.569)              | 0.0049  |
| SE (D) (n=432)             | -0.314±3.126   | -0.498±2.930  | 0.981 (0.905–1.063)              | 0.6385  |
| CCT (µm) (n=308)           | 558.240±54.016 | 574.111±66.418 | 1.005 (1.000–1.010)              | 0.0637  |
| POAG                       | 12 (3.09)      | 3 (4.80)     | 1.237 (0.341–4.489)              | 0.7465  |
| GS                         | 9 (2.32)       | 5 (6.33)     | 2.845 (0.927–8.731)              | 0.0676  |
| NVG                        | 8 (2.06)       | 3 (3.80)     | 1.875 (0.486–7.230)              | 0.3613  |
| Angle closure glaucoma     | 5 (1.29)       | 1 (1.27)     | 0.962 (0.11–8.523)               | 0.9870  |
| Secondary glaucoma         | 9 (2.32)       | 5 (6.33)     | 2.845 (0.927–8.731)              | 0.0676  |
| Right eye                  | 212 (54.64)    | 46 (58.23)    | 1.157 (0.709–1.889)              | 0.5590  |
| Previous uveitis history   | 23 (5.93)      | 9 (11.39)    | 2.040 (0.906–4.596)              | 0.0852  |
| Connective tissue disease  | 12 (3.09)      | 4 (5.06)     | 1.671 (0.525–5.322)              | 0.3850  |
| Thyroid disease            | 11 (2.84)      | 2 (2.53)     | 0.890 (0.193–4.097)              | 0.8813  |
| Kidney disease             | 11 (2.84)      | 2 (2.53)     | 0.890 (0.193–4.097)              | 0.8813  |
| Cancer                     | 19 (4.90)      | 3 (3.80)     | 0.767 (0.222–2.656)              | 0.6752  |
| BPH                        | 7 (1.80)       | 2 (2.53)     | 1.414 (0.288–6.937)              | 0.6692  |
| Tuberculosis               | 5 (1.29)       | 1 (1.27)     | 0.982 (0.113–8.523)              | 0.9870  |
| Cardiovascular problem     | 34 (8.76)      | 4 (5.06)     | 0.555 (0.191–1.612)              | 0.2792  |
| CVA                        | 12 (3.09)      | 2 (2.53)     | 0.814 (0.179–3.710)              | 0.7902  |
| HTN                        | 162 (41.75)    | 24 (30.38)   | 0.609 (0.362–1.024)              | 0.0615  |
| Family history of glaucoma | 4 (1.03)       | 3 (3.80)     | 3.789 (0.831–17.275)             | 0.0582  |
| DM                         | 197 (50.77)    | 29 (36.71)   | 0.562 (0.341–0.926)              | 0.237   |
| Diagnosis in study eye     |               |             |                                  |         |
| DME                        | 142 (36.60)    | 15 (18.99)   | ref                              |         |
| RVO                        | 114 (29.38)    | 26 (32.91)   | 2.159 (1.092–4.269)              | 0.0197  |
| Uveitis                    | 34 (8.76)      | 15 (18.99)   | 4.176 (1.862–9.366)              | 0.0076  |
| Others                     | 98 (25.26)     | 23 (29.11)   | 2.222 (1.104–4.472)              | 0.0150  |

OR, odds ratio; CI, confidence interval; OHT, ocular hypertension; AXL, axial length; SE, spherical equivalent; CCT, central corneal thickness; POAG, primary open-angle glaucoma; GS, glaucoma suspect; NVG, neovascular glaucoma; BPH, benign prostatic hyperplasia; CVA, cerebrovascular accident; HTN, hypertension; LASIK, laser-assisted in situ keratomileusis; LASEK, laser-assisted subepithelial keratectomy; DM, diabetes mellitus; DME, diabetic macular edema; RVO, retinal vein occlusion.

Data are presented as mean±standard deviation or n (%).

*Firth logistic regression was performed if there were zero observations.
nerve damage. To avoid steroid-induced OHT, many ophthalmologic studies have been conducted to determine its risk factors. However, there are few known risk factors, with controversial data for several of these factors.

Proposed risk factors for steroid-induced OHT include POAG, a first-degree relative with POAG, connective tissue disease, young age (<6 years), history of steroid-induced IOP elevation, penetrating keratoplasty (particularly Fuchs’ endothelial dystrophy or keratoconus), type 1 DM, and high myopia.

To date, however, there is little evidence of high myopia as a risk factor for steroid-induced OHT. One study, conducted in 1966, was subject to several limitations. First, it included only 17 participants. Second, among the 17 participants, 14 were aged <20 years. Since young age is a risk factor for steroid-induced OHT, adjustment using multivariable analysis would be necessary to make appropriate conclusions. Third, since high myopia was defined with refractive error, the true AXL was not presented. Moreover, to date, there has been no large-scale study to confirm those findings. The recent SAFODEX study was conducted to evaluate myopia as a risk factor for steroid-induced OHT; however, owing to insufficient AXL values, multivariable analysis could not be performed. The present study addressed these limitations, as we included a large sample (467 eyes) of patients for whom AXL values were recorded. Both univariable and multivariable models revealed that a long AXL was a significant risk factor for steroid-induced OHT (Tables 2 and 3). This is consistent with the results of the 1966 study.

Contrarily, a recent study revealed that a short AXL (<23.00 mm) may be a risk factor for steroid-induced OHT, which is inconsistent with our findings (Table 3). The inconsistency of these findings may be attributed to several reasons. First, the previous study had a relatively small sample of patients with myopia (84 eyes, all with an AXL <25 mm). Second, as both studies were cross-sectional, selection bias may have occurred in either or both. Third, our study lacked data from patients with an AXL <21 mm. Therefore, there is a need for further studies to determine the exact association between a short AXL and steroid-induced OHT.

It is unclear why a long AXL may be a risk factor for steroid-induced OHT. As POAG is a known risk factor for steroid-induced OHT, and as it is currently widely accepted that high myopia is associated with POAG, there may be several links between these variables. For example, patients with high myopia may have defective angle development or decreased permeability of the blood-aqueous barrier. However, there is a need for further research to determine the underlying mechanisms.

In addition to AXL, absence of DM was also a significant risk factor for steroid-induced OHT (Table 2). According to an analysis per different eye conditions, the risk of steroid-induced IOP was higher among patients with uveitis than among those with DME (Table 1). Although the reason for the potential relationship between DM and steroid-induced OHT is not known, it

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Table 2. Results of Multivariable Analysis Performed Using Factors That May Cause Steroid-Induced Ocular Hypertension

| Variables | Multivariable analysis (n=467) | \( OR \) (95% CI) | \( p \) value |
|-----------|-------------------------------|-----------------|-------------|
| Age       | 0.988 (0.971–1.005)           | 0.1741          |
| AXL       | 1.216 (1.004–1.472)           | 0.0452          |
| Sex (female) | 0.635 (0.382–1.057)           | 0.0807          |
| DM        | 0.570 (0.342–0.952)           | 0.0316          |

OR, odds ratio; CI, confidence interval; AXL, axial length; DM, diabetes mellitus. Multivariable analysis included variables that were significant in univariable analysis.

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Fig. 1. Distribution of the highest postoperative IOP according to axial length. The maximum postoperative IOP and AXL were analyzed via scatter plot analysis. The highest postoperative IOP was calculated for the AXL of each eye, and the trend line was analyzed. IOP, intraocular pressure; AXL, axial length.
seems that most patients with DM in our study had DME, which may be a protective factor against steroid-induced OHT.

A strength of our study is that all participants received the same type of steroid. DEX implantation is well-known to increase IOP.\textsuperscript{4,5,20-22} Therefore, it was reasonable to assess the risk of steroid-induced OHT among patients who have undergone intravitreal DEX implantation. Another major strength of our study is the large sample that was included, which allowed us to draw more definitive conclusions than researchers conducting smaller studies.

Nevertheless, this study also has several limitations, including its retrospective design and the fact that our findings cannot be directly compared to those of prospective, randomized controlled trials. Second, our study population did not include many patients with extremely short and long AXLs (<21 mm or >26 mm). Third, owing to the cross-sectional design, selection bias may have occurred.

Despite these limitations, however, our findings could be useful to clinicians in this field. As steroids are widely used and steroid-induced OHT is a major concern, our results demonstrate the need for clinicians to be more aware of steroid-induced OHT in patients with myopia. Specifically, we calculated a cut-off value of AXL of 23.585 mm, with an odds ratio of 2.355 (95% CI: 1.429–3.882, \(p=0.0008\)) (Table 3). Therefore, clinicians may consider administering steroids in patients with an AXL less than 23.585 mm and should be more cautious with patients with a higher AXL. These findings, however, need to be confirmed through large, randomized, prospective studies in the near future since the sensitivity and specificity of the cut-off values were not very high. Along with AXL, other known risk factors must also be evaluated for better predicting possibility of steroid-induced OHT.

In conclusion, we found that a long AXL is a risk factor for steroid-induced OHT and that clinicians should be aware of steroid-induced OHT when treating patients with high myopia with steroids.

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**AUTHOR CONTRIBUTIONS**

Conceptualization: Wungrak Choi, Gong Je Seong, and Min Kim. Data curation: Jung Dong Kim and Hyoung Won Bae. Formal analysis: Jung Dong Kim and Hyoung Won Bae. Funding acquisition: Wungrak Choi and Chan Yun Kim. Investigation: Wungrak Choi, Jung Dong Kim, Chan Yun Kim, and Min Kim. Methodology: Wungrak Choi, Jung Dong Kim, Hyoung Won Bae, and Min Kim. Project administration: Min Kim. Resources: Gong Je Seong and Min Kim. Supervision: Gong Je Seong and Min Kim. Validation: Jung Dong Kim and Hyoung Won Bae. Visualization: Gong Je Seong and Min Kim. Writing—original draft: Wungrak Choi, Gong Je Seong, and Min Kim. Writing—review & editing: Wungrak Choi, Gong Je Seong, and Min Kim. Approval of final manuscript: all authors.

**ORCID iDs**

Wungrak Choi https://orcid.org/0000-0002-3015-2502
Jung Dong Kim https://orcid.org/0000-0003-4023-9211

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**Table 3. Distribution of Steroid-Induced OHT according to AXL and Optimal Cut-Off Point**

| A. Number of patients with steroid-induced OHT in each group | AXL (mm) | OHT | Normal |
|---|---|---|---|
| <22 | 22 to <23 | 23 to <24 | 24 to <25 | 25 to <26 | ≥26 |
| OHT | 2 | 18 | 21 | 25 | 7 | 6 |
| Normal | 22 | 104 | 150 | 72 | 24 | 16 |

| B. Proportion of patients with steroid-induced OHT in each group | AXL (mm) | OHT | Normal |
|---|---|---|---|
| <22 | 22 to <23 | 23 to <24 | 24 to <25 | 25 to <26 | ≥26 |
| OHT | 8.33 | 14.75 | 12.28 | 25.77 | 22.58 | 27.27 |
| Normal | 91.67 | 85.25 | 87.72 | 74.23 | 77.42 | 72.73 |

| C. Optimal cut-off value of AXL for steroid-induced OHT using the Youden index | Cut-off point | AUC (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|
| ≥23.585, <23.585 | 0.6064 (0.5370–0.6758) | 63.29 (36.71–77.25) | 57.73 (51.54–81.44) |

| D. Proportion and odds ratio of steroid-induced OHT according to the optimal cut-off point | AXL (mm) | Total | Yes | OR (95% CI) | \(p\) value |
|---|---|---|---|---|---|
| <23.585 | 253 (54.18) | 224 (57.73) | 29 (36.71) | ref |
| ≥23.585 | 214 (45.82) | 164 (42.27) | 50 (63.29) | 2.355 (1.429–3.882) | 0.0008 |

AXL, axial length; OR, odds ratio; CI, confidence interval; OHT, ocular hypertension; AUC, area under the receiver operating characteristic curve.
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