The Relationship Between Long-term Use of Intranasal Corticosteroid and Intraocular Pressure

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Purpose: The purpose of this study was to investigate the association between long-term intranasal steroid use and intraocular pressure (IOP) elevation.

Patients and Methods: In total, 100 eyes from 50 patients on long-term intranasal steroids (> 2 y) for allergic rhinitis and 90 eyes from 45 controls were included in this study. Patients on other forms of steroids and risk factors for glaucoma were excluded. IOP was measured and non-mydriatic stereoscopic optic disc photos were taken for each eye. The vertical cup-to-disc ratio and the status of the optic disc were evaluated.

Results: The mean IOP for intranasal steroids group was significantly higher (15.24 ± 2.31 mm Hg) compared to the control group (13.91 ± 1.86 mm Hg; $P = 0.000$). However, there were no significant differences in the vertical cup-to-disc ratio and the status of glaucomatous optic disc changes between the groups.

Conclusions: Prolonged use of intranasal steroids cause statistical significant increase in IOP in patients with allergic rhinitis although no significant glaucomatous disc changes were seen. We suggest patients on long-term use of intranasal steroid have a yearly eye examination to be monitored for IOP elevation and those with additional risk factors for glaucoma is closely monitored for glaucoma.

Key Words: intranasal corticosteroid, intraocular pressure, glaucoma

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Intranasal corticosteroid (INC) has become a popular first-line treatment for various cases of rhinitis since beclomethasone nasal spray was introduced in 1973 for the treatment of hay fever.[1] As medical therapy advances, the emergence of newer generation of INC such as budesonide, fluticasone propionate, momethasone furoate, and triamcinolone acetonide are fast becoming popular choices because of their effectiveness.[2] INC are not only the first line of treatment for allergic rhinitis, but also for other diseases such as nasal polyposis, sinusitis, and post nasal surgery.[3–6]

Glaucoma has become the second cause of worldwide blindness after cataract according to World Health Organization (WHO) and the primary cause of irreversible blindness.[7] It is defined as a group of ocular diseases with characteristic optic nerve changes and visual dysfunction.[8,9] The pathophysiology of glaucomatous retinal ganglion cell death are multifactorial and intraocular (IOP) elevation has long been recognized as the key risk factor for the development and progression of glaucoma.[10,11]

Steroid-induced glaucoma (SIG) was first reported by Woods[12] in 1950 from his observation on patients using adrenocorticotrophic hormone (ACTH) and cortisone in the treatment of ocular inflammatory disease. Clinically, SIG has similarity with primary open angle glaucoma: IOP is usually elevated but the patients are largely asymptomatic. Often, the diagnosis of SIG is made retrospectively, when irreversible optic nerve damage has occurred.

There are several theories behind the pathophysiology of SIG. It is believed that steroids cause accumulation of mucopolysaccharides at the trabecular meshwork (TM) causing blockage of outflow,[13] increases the size of the TM cells to almost double its original size, increases the nuclear content, activate the endoplasmic reticulum and Golgi apparatus,[14,15] modifies the TM cytoskeleton, alters the arachidonic acid activity, and reduce phagocytic activity of the TM cells. These contribute to the accumulation of debris and impedes the aqueous outflow leading to SIG.[16]

Various forms of corticosteroid administration including oral, intravenous, intraocular, periocular, inhaled, and topical administration has been implicated to cause iatrogenic ocular hypertension and glaucoma.[17–22] However, the long-term effect of INC with IOP and glaucoma is not well documented. The available data regarding INC as a cause for secondary glaucoma are conflicting. Previous studies have relatively short duration of treatment of 2 years and showed INC has no ocular side effect and no significant correlation with IOP.[23–26] The possibility of INC causing an increase in IOP and subsequent glaucoma is of concern because of the possible blinding ocular sequelae.[27] Furthermore, there is a steady increase of INC being prescribed every year especially among children and young adults,[28] the most susceptible group of patients for steroid responsiveness. Although the bioavailability after nasal administration are said to be very low, a single dose of nasal route absorption can be as high as 50%.[29,30] We aim to assess the relationship between long-term use of INC for at least 2 years with IOP and the risk of developing glaucoma.

METHODS

This is an observational cross-sectional study in a tertiary referral center from December 2015 to October 2016. Using a convenience sampling method, all patients from 10 to 40 years of age who have been using INC for a minimum duration of

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2 years attending the rhinitis clinic were invited to join the study. Individuals with preexisting glaucoma, those receiving other types of steroids topically or systematically other than nasal steroids, had a previous ocular injury or eye surgery or with ongoing ocular infections or inflammation were excluded. Data collected include age, sex, underlying medical illness, indications for nasal steroids; types, frequency, and the dose of nasal steroids; and family history of glaucoma. All patients in this study are on INC for allergic rhinitis. Control group were healthy volunteers from Ophthalmology clinic staffs who were not on any type of steroids medication. Ethical approval was obtained from the Universiti Kebangsaan Malaysia Research and Ethics Committee (Ethical approval code: FF-2015-370). This study adhered to the tenets of the Declaration of Helsinki and Malaysian Guidelines for Good Clinical Practice (GCP). A signed written informed consent was obtained from all patients or legal guardians prior to enrollment.

Intraocular Pressure (IOP) Measurement

IOP of both eyes of each patient was measured using slit-lamp mount calibrated Goldmann applanation tonometer (Haag-Streit Diagnostics) by a single examiner who was not masked to the state of the patients. A new fluorescein strip was used to stain the ocular surface for each patient. Just adequate amount of fluorescein was applied to ensure appropriate mires thickness when applanated at the corneal apex using a 3.06 mm tonometer head. The examiner's fingers were ensured not to press on the patients' eyeball to prevent falsely high IOP.

Evaluation of Vertical Cup-to-disc Ratio (VCDR) and Glaucoma Status of the Optic Disc

After IOP measurement, stereoscopic nonmydriatic optic disc photos were taken using Canon digital retinal camera CR-2 PLUS. Fundus photographs were reviewed independently by the principal investigator and coinvestigator using a stereoscopic viewer, assessing any signs of glaucomatous optic disc features such deep cupping, bayonetting, VCDR of >0.7 and rim notching. The evaluation of the optic disc for any glaucomatous changes was done by a masked single experienced glaucoma consultant. Patients with IOP of >21 mm Hg and glaucomatous optic disc changes were referred to the ophthalmology clinic for further glaucoma assessment.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, Version 23. Demographic data and the IOP differences between the two groups were analyzed with independent *t* test. Subgroup analyses were calculated using χ^2 for categorical data and one-way ANOVA to compare readings in >2 groups. The predictive factors for increased IOP were determined using multiple linear regression analysis. *P*-values of <0.05 were considered statistically significant.

RESULTS

Demographics

In total, 102 eligible patients were identified; 49 patients did not consent or was not compliant with INC use. Two patients were excluded for concomitant use of topical steroid and one had poor optic disc photo. Fifty patients on long-term INC and 45 controls were therefore included in the final analysis. There was no significant age difference between the 2 groups (Table 1). The age range was 10 to 40 in both the INC and the control group. There was a slight male preponderance in the INC group with a male to female ratio of 1.3:1. However, this ratio reverses in the control group with the male to female ratio of 1:2.2. The mean duration of INC use was 5.42 ± 3.22 years with 44% of them using >5 years duration. Most of the patients use mometasone furoate (78%), followed by fluticasone furoate (12%), and beclomethasone dipropionate (10%); 80% of them use once daily dose. None of the patients has a family history of glaucoma.

TABLE 1. Characteristics of Intranasal Corticosteroid and Control Group

	n (%)		
	INC	**Control**	***P***
Age (mean ± SD) (y)	22.88 ± 10.89	26.49 ± 7.46	0.061*
Sex	Male: 28 (56)	Male: 14 (31.1)	0.012†
	Female: 22 (44)	Female: 31 (68.9)	
IOP (mean ± SD) (mm Hg)	RE: 15.30 ± 2.493	RE: 13.96 ± 1.770	0.003*
	LE: 15.18 ± 2.145	LE: 13.87 ± 1.961	0.002*
Duration of INC use (mean ± SD)	Mean 5.42 ± 3.22	NA	
Dose of INC	Once daily: 40 (80) Twice daily: 10 (20)	NA	
Type Of INC	Momethasone: 38 (78) Fluticasone: 6 (12) Beclomethasone: 5 (10)	NA	

*Independent *t* test.
†χ^2 test.
INC indicates intranasal corticosteroid; NA, not applicable.

Intraocular Pressure and Optic Disc Changes

Data analysis was done for 100 eyes in the INC group and 90 eyes in the control group (Table 2). The IOP measurement was done between 9 am to 10 am in the morning for all patients and the majority of control subjects. Only about less than a quarter of controls (10/45 controls) had their IOP taken in the late afternoon, most of them being medical students. The IOP data was tested for normality by Shapiro-Wilk test and histogram and found to be normally distributed mean IOP in the INC group was significantly higher (15.24 ± 2.314 mm Hg) compared with the control group (13.91 ± 1.858 mm Hg; $P = 0.000$). There was no

TABLE 2. IOP, VCDR, and Glaucomatous Optic Disc Changes in Control and Intranasal Corticosteroids Group

	Case n = 100	**Control n = 90**	***P***
IOP (mean ± SD) (mm Hg)	15.24 ± 2.314	13.91 ± 1.858	0.000*
VCDR (mean ± SD)	0.38 ± 0.1344	0.38 ± 0.1443	0.976*
Glaucomatous disc changes‡ [n (%)]	16 (16)	7 (7.8)	0.083†

*Independent *t* test.
†χ^2 test.
‡Changes such as rim notching, bayoneting, and nasalization.
IOP indicates intraocular pressure; VCDR, vertical cup to disc ratio.

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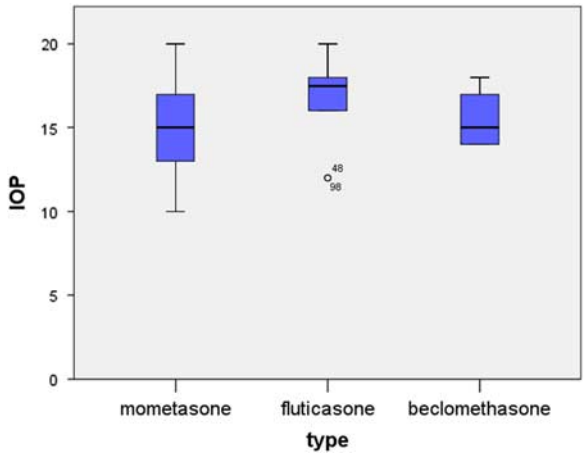

FIGURE 1. Boxplot representing IOP distribution in different types of intranasal corticosteroids. Figure 1 can be viewed in color online at www.glaucomajournal.com.

statistically significant difference in the measurement of the VCDR between groups. Although 16 (16%) eyes in the INC group had glaucomatous disc changes, only 7 eyes (7.8%) have these changes in the control group, although this was not found to be statistically significant ($P = 0.083$).

We also reanalyze 50 eyes in the INC group and 45 eyes in the control group which were randomly taken using Randomization.com software. The mean IOP in the INC and control groups were 15.08 ± 2.346 mm Hg and 13.84 ± 1.89 mm Hg respectively ($P = 0.006$). There were still no statistical differences in the proportion of eyes with glaucomatous disc changes or VCDR.

Figure 1 shows the distribution of IOP measurement on patients using different types of INC. While the mean IOP in patients using fluticasone appears to be higher (16.67 ± 2.42 mm Hg) than mometasone (14.97 ± 2.29 mm Hg) and beclomethasone (15.60 ± 1.77 mm Hg), this difference was not statistically significant ($P = 0.053$), possibly because of the small number of patients in each group.

Factors Affecting IOP

A simple linear regression analysis showed that age and the use of INC are significantly associated with IOP elevation. The use of INC increases the IOP by 1.3 mm Hg (95% CI, 0.72-1.9; $P < 0.001$). There was also a negative association between age and IOP (regression coefficient $= -0.04$; $P = 0.08$, Table 3. Multiple linear regression analysis was done to evaluate the association of IOP with the use of intranasal steroids, age, dosage, duration, and type of intranasal steroids. We found that after adjusting for age, the use of long-term intranasal steroids increases the IOP by a mean of 1.212 mm Hg compared with controls ($P < 0.01$). Sex, dose, duration, and types of intranasal steroids had no statistically significant association with IOP.

TABLE 3. Relationship Between Intraocular Pressure With Usage of Intranasal Corticosteroids, Age, Dose, Duration, and Type of Intranasal Steroids

Variable	Regression Coefficient (95% CI)	P*
Use of nasal corticosteroids	1.328 (0.724, 1.934)	0.000
Age	−0.044 (−0.771, −0.012)	0.008
Sex	0.98 (−0.20, 1.068)	0.18
Dose	−0.170 (−0.857, 0.515)	0.622
Duration	−0.237 (−0.168, 0.121)	0.746
Type	0.582 (−0.122, 1.287)	0.104

*Univariate linear regression.

DISCUSSION

Patients with rhinitis occupy the main bulk of cases seen in the otorhinolaryngology clinics in most hospitals. In the United States, approximately 30% of adult and 40% of children are affected every year.[27] In our center, the prescription for intranasal mometasone furoate almost doubled within a year.

The diverse and profound effects of corticosteroids on the inflammatory cascade are responsible for its high efficacy in the treatment of allergic rhinitis.[29] The effect of INC on the IOP varies. Although some authors report a high safety profile, other studies found a significant increase in the IOP with INC use. Bross-Soriano et al in his prospective placebo-controlled study on the effects of 3 INC on IOP within 1 year period revealed insignificant correlation.[23] Spiliotopoulos et al[24] also found no statistically significant increase in IOP in 54 patients on nasal dexamethasone spray after 1 month. Ozkaya et al[25] found no ocular side effects in children prescribed with intermittent nasal steroid spray for 2 years. In addition, the effect of INC to IOP in 9 patients with ocular hypertension or controlled glaucoma was found to be insignificant compared with placebo group.[26]

Dreyer[31] in 1993 reported 3 cases of glaucoma requiring trabeculectomy following 6 months use of nasal and inhaled corticosteroids. Two years later, another 3 cases of nasal and inhaled corticosteroids induced glaucoma was described by Optatowsky et al,[32] with one of them having IOP elevation of > 15 mm Hg above baseline. Later in 1997, a large case-control study involving nearly 10,000 cases and 38000 controls revealed a significant correlation between inhaled and nasal corticosteroids with raised IOP, with an odd ratio of 1.44.[20]

We evaluated the IOP in our mostly Asian patients who have used INC for at least 2 years. Our groups of patients are fairly young and more susceptible to steroid responsiveness. However, none of our patients have any family history of glaucoma. We found significantly higher IOP in these patients compared with their age-matched controls although this increased IOP still falls within the normal range and was not sufficient to cause significant glaucomatous optic disc changes between the 2 groups.

We found the mean IOP in patients receiving fluticasone was highest compared with the other 2 types of INC although not statistically significant, possibly because of the small number of patients in each group.

We also found statistically higher IOP in younger patients on INC. The effect of corticosteroid on IOP is not just dose but also age-dependent.[33] Younger patients receiving INC are more at risk of developing higher IOP. We acknowledged that the difference in IOP between the INC and control groups may not be clinically significant though it is statistically significant, especially when the optic nerves are healthy with an average CD ratio of 0.3 in our study population. Although the dose of inhaled steroid in this intranasal steroids preparation is minimum, these patients may have used it for many years. If the minimum use of two years has revealed an approximately 1 mm Hg

increment, there may be some concern that the IOP may increase exponentially as years go by. Previous studies have shown younger age and longer duration of steroid use are strong predictors of IOP elevation.[33] In addition, some patients with allergic rhinitis also have other atopic diseases such as bronchial asthma and skin eczema requiring concomitant steroid therapy in different modes of administration, that is, inhaled or topical. The cumulative dose together with INC may increase the risk of ocular hypertension and glaucoma.[20]

As with other cross-sectional studies, the limitations of this study restrict the extrapolation of data. A prospective observational study may show if the IOP elevation is in fact significantly elevated from the pretreatment IOP. Assessment of glaucoma is solely based on optic disc appearance alone without Humphrey visual field tests or optical coherent tomography of the optic discs. Thus, the possibility of patients having undiagnosed glaucoma is not known. Other sources of bias such as the difference in time of IOP measurement in a small proportion of controls, sex, and masking of the investigator measuring the IOP are also significant limitations in this study.

The results of our study suggest that prolonged use of INC may have a cumulative effect on the IOP. For susceptible patients who have been on prolong use of INC, we suggest them to be screened for IOP elevation and glaucoma. The need for screening is especially important in the presence of additional risk factors for glaucoma such as any family history of glaucoma and myopia.

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