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Intranasal corticosteroids do not lead to ocular changes: a systematic review and meta-analysis

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Abstract

Objective—The safety and efficacy of intranasal corticosteroids (INCS) are well established, but there remains apprehension that INCS could lead to systemic side effects, as with oral steroids. The objective of this systematic review was to assess whether the use of INCS lead to increased intraocular pressure (IOP) above 20 mmHg, glaucoma, or formation of posterior subcapsular cataracts in adult patients with rhinitis.

Methods—Two medical librarians searched the published literature for records discussing the use of “nasal steroids” in “rhinitis” and their effect on “intra-ocular pressure”, “cataracts”, or “glaucoma”.

Results—A total of 484 studies were identified and 10 randomized controlled trials met our inclusion criteria. Meta-analysis of 2,226 patients revealed that the relative risk of elevated IOP in those who received INCS was 2.24 (95% CI 0.68 – 7.34) compared to placebo. The absolute increased incidence of elevated IOP in patients using INCS compared to placebo was 0.8% (95% CI 0% – 1.6%). There were zero cases of glaucoma in both placebo and INCS groups at 12 months. The absolute increased incidence of developing a posterior subcapsular cataract was 0.02% (95% CI –0.3% – 0.4%).

Conclusion—Use of INCS is not associated with a significant risk of elevating IOP or developing a posterior subcapsular cataract in patients with allergic rhinitis. Presence of glaucoma, however, is the real clinical adverse event of concern. There were zero reported cases of glaucoma at 12 months. Future studies should formally evaluate for glaucoma rather than use IOP measures as a surrogate.

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Keywords

intranasal steroids; intraocular pressure; glaucoma; cataract formation

INTRODUCTION

Intranasal corticosteroids (INCS) are a well-established and effective treatment for allergic rhinitis.¹ The nasal mucosa has a large surface area with receptors that can bind to high drug concentrations.² Glucocorticoids suppress many stages of the inflammatory process by affecting cells and cytokines that play key roles in allergic inflammation, thereby reducing nasal blockage, rhinorrhea, sneezing and nasal itching.^{2–12} The American Academy of Otolaryngology- Head and Neck Surgery guidelines strongly recommend use of INCS in patients whose allergic rhinitis symptoms affect their quality of life.¹

While the safety and efficacy of INCS are well established; there remains a concern that use of INCS can lead to systemic side effects, as seen with oral administration of steroids. For example, prolonged treatment with oral steroids can increase the risk of posterior subcapsular cataracts or open-angle glaucoma.^{13,14} The concern that INCS may lead to the same adverse effects seen with oral corticosteroids stems from only a few case reports describing ocular changes in patients who already had near abnormal or elevated intraocular pressure (IOP) baseline values using INCS. Furthermore, some of these patients used inhaled corticosteroids in addition to INCS.^{15,16} Despite the overwhelming evidence that INCS does not lead to an increased risk of glaucoma or cataract formation,^{17–19} there have been no meta-analyses conducted on ocular changes, and only a handful of review articles that discuss the use of INCS and ocular changes.^{20–24}

The primary objective of this systematic review and meta-analysis was to assess whether the use of INCS leads to an increase in IOP above 20 mmHg. The secondary objective was to assess whether use of INCS leads to the presence of glaucoma or development of posterior subcapsular cataracts in adult patients with allergic rhinitis.

METHODS

PRISMA guidelines were followed for this study.²⁵ No review protocol was published. Studies were selected using the PICOS (population, interventions, comparators, outcomes, and study design) format: 1) Population: patients aged 12 years old or older suffering from a diagnosis of rhinitis, 2) Intervention: intranasal steroids, 3) Comparison: placebo, 4) Outcome: increase in IOP above 20 mmHg, formal evaluation for glaucoma, or formation of posterior subcapsular cataract, 5) Study design: randomized controlled trials (RCTs). IOP was chosen as one of the outcome measures because elevated values of IOP are one of several risk factors for glaucoma²⁶ and represent the primary goal of current glaucoma treatment.²⁷ Normal IOP is historically defined within the range of 10-21 mmHg.²⁸ Given that less than 10% of patients with abnormal IOP values between 21-32 mmHg progress to primary open angle glaucoma,²⁹ a formal evaluation of glaucoma was also included as an outcome measure. Our search strategy excluded children 12 years and younger, as both glaucoma and cataracts are a cumulative process that tends to develop later in life, and the

likelihood of seeing any clinically significant changes in children is small. Any duration of intranasal steroid use met eligibility criteria for this review to provide a wide range of time points for the meta-analysis. Studies that included patients with baseline glaucoma were eligible, as were studies using any type of tonometer.

Two medical librarians searched published literature for records discussing the use of “nasal steroids” in “rhinitis” and their effect on “intra-ocular pressure,” “cataracts” or “glaucoma.” The librarians created search strategies using a combination of keywords and controlled vocabulary in Ovid Medline 1946-, Embase 1947-, Scopus 1823-, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and [Clinicaltrials.gov](https://www.clinicaltrials.gov) 1997-. All search strategies were completed in August 2017, and a total of 680 results were exported to a reference manager software (EndNote X8). 347 duplicate records were identified using the automatic duplicate finder in EndNote, resulting in 182 records being removed. An additional 14 duplicate records were discovered and removed following the initial Endnote de-duplication, allowing for a total of 484 unique citations included in the project library. The literature search was executed again in February 2018 in Ovid Medline, Embase, Scopus, Cochrane Library, and [Clinicaltrials.gov](https://www.clinicaltrials.gov). A total of 34 additional results were retrieved, and de-duplicated using Endnote. A total of 17 unique records were added to the pool of citation results. Fully reproducible search strategies for each database can be found in the appendix.

Study Selection

Two authors (C.V.V and J.C.L.) independently screened the studies to identify eligible articles (Figure 1). Titles and abstracts were first reviewed for study inclusion. At this level, studies were excluded if: 1) patients were less than 12 years of age, 2) patients did not have a diagnosis of rhinitis, 3) patients used systemic, oral, or inhaled steroids, or 4) the study designs were not RCTs. Next, full texts were reviewed. Studies were excluded if: 1) studies did not report IOPs, presence of glaucoma, or evidence of posterior subcapsular cataract formation, 2) studies were not RCTs, 3) studies were duplicates, or 4) studies were non-English. Any discrepancies were addressed and resolved with the senior author (J.E.C.L.).

Data extraction and summary measures

Our primary outcome variable was the rate of elevated IOP above 20 mmHg. Our secondary outcome variable was the presence of glaucoma or posterior subcapsular cataract formation. Values of IOP, presence of glaucoma, and grading of cataract formation were extracted. A random effects meta-analysis was performed to summarize the relative risk from each study and to calculate an overall relative risk of the effect of intranasal steroid use on the risk of elevated IOP (defined as IOP greater than 20 mmHg or more than 7 mmHg increase from baseline). The I^2 statistic was used to evaluate statistical heterogeneity. All analyses were performed in STATA statistical software version 14.2 (STATA Corporation, College Station, TX). While a meta-analysis was unable to be performed for the incidence of elevated IOP, presence of glaucoma, or presence of posterior subcapsular cataract formation due to the differences in the way data were reported in the included studies, the incidence of these outcomes was calculated and reported.

Quality Assessment

Assessment of risk of bias was independently performed by two authors (C.V.V. and J.C.L.) using the Cochrane Risk of Bias Tool.³⁰ Domains pertaining to: 1) sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, and 5) selective outcome reporting were assessed for all studies that met inclusion criteria. The domains were scored as low risk, high risk, or unclear risk of bias (Figure 2). Any discrepancies were addressed and resolved with the senior author (J.E.C.L.).

RESULTS

Characteristics of Included Studies

The search strategy resulted in 501 studies after excluding duplicates. 10 studies satisfied our inclusion and exclusion criteria (Figure 1). These studies were all RCTs with no heterogeneity, making this systematic review and meta-analysis level 1A evidence. Based on varied time points that assessed IOPs between studies, and the number that reported data in a manner allowing for meta-analysis, only four of the studies were used for the meta-analysis. Among these studies, a shared time point of 52 weeks was chosen for assessing whether use of intranasal steroids increased IOP to values above 20 mmHg. The included studies are denoted in Table 1 and shown in the forest plot in Figure 3.

Quality Assessment

Quality assessment is shown in Figure 2 for all included articles in the systematic review and meta-analysis. Overall, risk of bias ranged from low to unclear for the majority of the domains across the included studies. Of these randomized controlled trials, seven studies had at least one domain of high risk of bias. Specifically, Chervinsky et al.³¹ for allocation concealment, La Force et al.³² for incomplete outcome data, Ratner et al.³³ for selective reporting, Bross-Soriano et al.³⁴ for allocation concealment and selective reporting, Weinstein et al.³⁵ for incomplete outcome data, Rosenblut et al.³⁶ for selective reporting, and Berger et al.³⁷ across all domains except for random sequence generation.

Systematic Review

The characteristics of the studies included in the systematic review are shown in Tables 1 -3. Table 1 reports the absolute increased incidence of elevated IOP among the included studies, Table 2 reports the incidence of glaucoma, and Table 3 reports the absolute increased incidence of posterior subcapsular cataract. Overall, the patient population included patients older than 18 years of age, except for the studies conducted by Berger et al.³⁷ and Igarashi et al.³⁸ which included adolescents. All patients had a diagnosis of rhinitis. There were no patients with pre-existing glaucoma or with evidence of posterior subcapsular cataract formation prior to the use of INCS except for two patients in the Berger et al.³⁷ study who were found to have posterior subcapsular cataracts at baseline which were initially missed. There were two studies that included patients with IOPs above 21 mmHg at baseline.^{35,36} The included studies were conducted across the world including the United States, Canada, and India. There were only two studies^{37,39} that assessed ocular changes with first

generation INCS (beclomethasone). The majority of studies mentioned use of tonometry to assess IOPs but the exact tools were varied and included use of a noncontact tonometer,³⁸ tonopen,³⁹ Goldmann applanation tonometer.^{34,40} Only one study obtained IOP measurements at the same time of day.³² The absolute increased incidence of elevated IOP in patients using INCS was 0.8% (95% CI: 0% to 1.6%), which was not significant. There were five studies^{31,32,35–37} that formally assessed for the presence of glaucoma (Table 2) using slit-lamp examination^{31,36,37} and/or visual acuity.^{31,32,35} The overall incidence of glaucoma was 0/2837, with a one-sided upper 95% confidence limit of 0.1% as calculated by Rumke's rule.⁴¹ Among the four studies that assessed for posterior subcapsular cataract formation, only two studies^{31,40} used the Lens Opacity Classification System (LOCS III),⁴² while the other two studies^{37,38} used an ophthalmologist or licensed optometrist to perform a fundoscopic examination. The absolute increased incidence of patients developing a posterior subcapsular cataract while using INCS versus placebo was not significant (Table 3). The absolute increased incidence was 0.02% with 95% confidence interval –0.3% to 0.4%.

Meta-Analysis

Table 1 describes the characteristics of the included studies from which the data for the meta-analysis were extracted. The studies were performed in various locations around the world, and all were multicenter trials. All patients were at least 12 years of age, with at least a two-year history of perennial allergic rhinitis (PAR), if not longer. There were no patients with pre-existing glaucoma. All compared a second-generation INCS to placebo. The primary outcome of interest was safety, which included IOPs. The definition of elevated IOP across these studies was at least greater than 20 mmHg. The majority of the studies reported least squares mean changes from baseline for the average IOP between both eyes versus per eye.

In total, the overall sample size was 2,226 patients (range 245 – 806), with 1,587 receiving the study drug and 639 in the placebo group. All studies shared a follow-up period at 52 weeks. Meta-analysis revealed that the overall pooled relative risk of abnormally elevated IOP in those who received INCS was 2.24 (95% CI 0.68 – 7.34) compared to those who received placebo. The overall statistical heterogeneity was very low, with an I^2 of 0% (Figure 3).

DISCUSSION

This systematic review and meta-analysis revealed no statistically significant increased risk of elevated IOP in patients using INCS compared to those using placebo or increase in incidence. The overall incidence of glaucoma was 0/2837, with a one-sided upper 95% confidence limit of 0.1% as calculated by Rumke's rule.⁴¹ There was no statistically significant increase in the incidence proportion of patients developing a posterior subcapsular cataract while using INCS versus placebo. Overall, these findings demonstrate that the use of INCS does not lead to clinically significant ocular changes in patients using INCS versus placebo.

Glaucoma is characterized as an optic neuropathy that is the leading cause of irreversible blindness in the world.^{26,43} Open angle glaucoma accounts for approximately 80% of all the glaucoma cases seen in the United States.⁴⁴ The risk factors for developing visual field defects attributed to open angle glaucoma are multifactorial, they include: age, larger vertical or horizontal cup-disc ratio, higher IOP, thinner central corneal thickness, gender, and cardiovascular disease.^{45,46} While elevated IOP is a risk factor for glaucoma, patients with normal IOP can also present with glaucoma. For example, the Baltimore Eye Study followed 97 patients with untreated glaucoma, finding that more than half (55%) of the patients with glaucoma would have been missed with screening tonometry because their IOPs were less than 21 mmHg.⁴⁷

The majority of RCTs assessing ocular changes in patients using INCS have used IOP measures to assess the safety of INCS, but this measure is ineffective in diagnosing optic nerve damage.⁴⁷ Instead, formal ocular examinations would be a more accurate means of determining the presence and progression of glaucoma. Among the few RCTs that conducted formal ocular examinations for glaucoma in patients using INCS, the incidence was 0/2837, upper limit 95 % CI 0.1%.

A secondary objective of this study was to assess for development of posterior subcapsular cataract. Cataract development is defined as any opacity or cloudiness of the crystalline lens.⁴⁸ Cataracts are usually graded with the LOCS III classification system, which is based on a set of standard color photographic transparencies of cortical cataract (C), nuclear opalescence (NO), posterior subcapsular cataract (P), and nuclear color (NC).⁴² Based on the studies included in this systematic review, the absolute increased incidence of developing a posterior subcapsular cataract was not significant (incidence proportion 0.02% (95% CI: -0.3% to 0.4%).

A strength of this study was only using RCTs, which helps with causal inference and minimizes risk of confounding. From these studies, a long follow-up period of 52 weeks was used in the meta-analysis, and the sample size of 2,226 patients was large. A significant limitation of this meta-analysis, however, is that IOP measures are not accurate surrogates to assess the safety of INCS. Rather, formal evaluations of the eye through slit-lamp examination and visual acuity testing are more informative and accurate in diagnosing glaucoma, which was the main ocular safety concern among the RCTs included in this meta-analysis. Additionally, the tools used for tonometry among included studies were varied in spite of having a gold standard tool (Goldmann Applanation Tonometer). The times that the IOP measures were obtained were also varied, with the exception of one study.³² It is well established that IOP varies throughout the day, with changes up to 6.8 mmHg,⁴⁹ thus it is possible that some patients with IOPs above 20 mmHg were false positives. Therefore, tonometry should not have been used as a surrogate to demonstrate whether INCS lead to glaucoma, as has been seen with oral corticosteroid administration.

Importantly, in all the RCTs included in this systematic review, the patients at highest risk for progressing to glaucoma were excluded from the study. Those patients who have diabetes, pre-existing glaucoma, high baseline IOP, or cardiovascular disease are the ones that are likely most susceptible to glaucomatous changes, and represent the population about

which both ophthalmologists and otolaryngologists may be most concerned when starting INCS. Thus, while we found no significant differences between INCS users and those using placebo, our study is limited in its generalizability, and highlights the need to formally assess any ocular changes in high risk patient populations starting INCS to see if our findings are consistent in that population as well.

CONCLUSION

Use of INCS is not associated with a significant risk of elevating IOP or developing a posterior subcapsular cataract in patients with allergic rhinitis. Presence of glaucoma, however, is the real clinical adverse outcome of concern. There were 0 reported cases of glaucoma at 12 months (incidence 0/2837, upper 95% confidence limit 0.1%). Future studies should formally evaluate for glaucoma rather than use IOP measures as a surrogate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PRISMA 2009 Flow Diagram

Figure 1.
PRISMA Flow Diagram

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Chervinsky 2007	+	-	?	?	+	?
La Force 2013	+	?	?	?	-	+
Ratner 2006	?	?	?	?	?	-
Bross Soriano 2004	+	-	?	?	?	-
Weinstein 2014	?	?	+	+	-	?
Rotenberg 2011	+	+	+	+	+	+
Igarashi 2012	?	?	?	?	+	?
Rosenblut 2007	+	+	?	?	+	-
Berger 2014	+	-	-	-	-	-

Figure 2.

Risk of Bias assessed using the Cochrane Risk of Bias tool. The (+) symbol represents a low risk of bias, the (-) symbol represents a high risk of bias, and the (?) symbol represents an unclear risk of bias.

Figure 3.

Meta analysis of randomized controlled trials demonstrating no significant increase in intra ocular pressures. RR, Relative risk; CI, Confidence interval; IOP, intraocular pressure

Table 1

Absolute increased incidence of elevated IOP among included RCTs

Study	Sample Size	Intranasal drug and daily dose	Follow-up Time (weeks)	Number of patients with elevated IOP
Berger et al. 2014	611	MP29-02 (548 mcg of azelastine hydrochloride and 200mcg of FP) vs. FP 200mcg	24, 48	Absolute number not reported
Bross-Soriano et al. 2004	360	FP 200mcg vs. MFNS 200 mcg vs. BDP 400 mcg vs. placebo	3, 6, 12, 24, 48	‡ 0 patients
‡ Chervinsky et al. 2007	663	Ciclesonide 200 mcg vs. placebo	24, 48, 52	Absolute number not reported
Igarashi et al. 2011	11	MFNS 200mcg vs. placebo	2, 4	‡ 0 patients
‡ La Force et al. 2013	512	FFNS 110 mcg vs. placebo	12, 24, 36, 52, 64, 76, 88, 194	¶ 7 patients using FFNS and 1 patient using placebo
Man et al. 2013	23	FP 3mg/240mL isotonic saline	6	‡ 0 patients
Ratner et al. 2006	726	Ciclesonide 25 mcg vs. ciclesonide 50 mcg vs. ciclesonide 100 mcg vs. ciclesonide 200 mcg vs. placebo	4	‡ 8 patients using ciclesonide and 3 patients using placebo
‡ Rosenblut et al. 2007	806	FFNS 110 mcg vs. placebo	12, 24, 52	§ 12 patients in FFNS, 0 patients in placebo group
Rotenberg et al. 2011	60	Saline irrigations 240mL vs. saline irrigations 240mL with budesonide 256 mcg vs. saline irrigations 240mL with 1000 mcg budesonide	24, 48	‡ 0 patients
‡ Weinstein et al. 2014	245	BDP 320 mcg vs. placebo	30, 52	Absolute number not reported
Overall Trend	Total n =2498	Nasal steroid (n=1866) vs. placebo (n=632)	Incidence proportion of elevated IOP in those using INCS vs. placebo: 0.8% (95% CI: 0% to 1.6%)	

Abbreviations: MP29-02 = Azelastine hydrochloride with fluticasone propionate, FP= fluticasone propionate, FFNS = fluticasone furoate nasal spray, BDP= Beclomethasone dipropionate, MFNS = mometasone furoate nasal spray.

‡ Studies included in meta-analysis.

‡ Elevated IOP is defined as IOP greater than or equal to 20 mmHg,

§ greater or equal to 21 mmHg,

¶ or greater than a 7 mmHg increase in baseline IOP. Only the studies that reported absolute numbers of elevated IOP are reflected in the total number of patients in the ICNS and placebo groups. n= number of patients.

Table 2

Incidence of glaucoma among included RCTs

Study	Sample Size	Treatment group	Baseline Glaucoma	Glaucoma at 12 months in treatment group (s)
Berger et al. 2014	611	MP29-02 548 mcg/200 mcg vs. FP 200 mcg	0 cases	0 cases
Chervinsky et al. 2007	663	Ciclesonide 200 mcg vs. placebo	0 cases	0 cases
Rosenblut et al. 2007	806	FFNS 110 mcg vs. placebo	0 cases	0 cases
Weinstein et al. 2014	245	BDP 320 mcg vs. placebo	0 cases	0 cases
La Force et al. 2013	512	FFNS 110 mcg vs. placebo	0 cases	0 cases
Overall Trend	Total n=2837 patients	Nasal steroid (n=2198), placebo (n=639)		Incidence: 0/2837 (upper 95% confidence limit =0.1%)

Abbreviations: MP29-02 = Azelastine hydrochloride with fluticasone propionate, FP= fluticasone propionate, FFNS = fluticasone furoate nasal spray, BDP= beclomethasone dipropionate. n= number of patients.

Table 3

Incidence of posterior subcapsular cataract among included RCTs

Study	Total sample size	Treatment group	Posterior subcapsular cataract
Berger et al. 2014	611	MP29-02 548 mcg/200 mcg vs. FP 200 mcg	1 patient using MP29-02 and [†] 1 patient using FP
Chervinsky et al. 2007	663	Ciclesonide 200 mcg vs. placebo	0 cases
Rosenblut et al. 2007	806	FFNS 110 mcg vs. placebo	2 patient using FFNS and 1 patient using placebo
Weinstein et al. 2014	245	BDP 320 mcg vs. placebo	0 cases
Man et al. 2013	23	FP 3mg/240mL isotonic saline	0 cases
La Force et al. 2013	512	FFNS 110 mcg vs. placebo	0 cases
Overall Trend	Total n= 2860	Nasal steroid (n=2,221) vs. placebo (n=639)	Incidence proportion of posterior subcapsular cataract in those using INCS vs. placebo: 0.02% (95% CI: -0.3% to 0.4%)

Abbreviations: MP29-02 = Azelastine hydrochloride with fluticasone propionate, FP= fluticasone propionate, FFNS = fluticasone furoate nasal spray, BDP= beclomethasone dipropionate. n= number of patients.

[†]Two patients were found to have posterior subcapsular cataracts that were present at screening and these patients were randomized in error; this number is not reflected in the above table.