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# Intranasal corticosteroids do not affect intraocular pressure or lens opacity: a systematic review of controlled trials\*

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*Rhinology* 53: 0-0, 2015

DOI:10.4193/Rhino15.020

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\*Received for publication:

February 5, 2015

Accepted: May 11, 2015

## Abstract

**Background:** Intranasal corticosteroids (INCS) are prescribed for the long-term prophylactic treatment of inflammatory upper airway conditions. Although some systemic absorption can occur via topical routes, the clinical relevance is controversial. The effects of orally administered corticosteroids on intraocular pressure (IOP) and lens opacity (LO) are well established, but the impact of the INCS is less well defined. This study aims to systematically review the literature for evidence of adverse ocular events with INCS use.

**Methodology:** A systematic review of literature from Medline and Embase databases (January 1974 to 21st of November 2013) was performed. Using the PRISMA guidelines, all controlled clinical trials of patients using INCS, that reported original measures of IOP, LO, glaucoma or cataract incidences were included. Studies with adjuvant administration of oral, inhaled and intravenous steroids were excluded.

**Results:** 665 articles were retrieved with 137 were considered for full-text review. Of these, 116 (85%) were literature reviews and two were case reports. 19 studies (10 RCTs, 1 case-control, 8 case series) were included for the qualitative review, of which 18 reported data on IOP and 10 on cataract/LO. None (n=0) of the 10 RCT reporting data on glaucoma or IOP demonstrated changes in IOP compared to control. Also none (n=0) of the 6 RCTs reporting cataract or lens opacity demonstrated changes compared to control.

**Conclusion:** Data from studies with low levels of bias, do not demonstrate a clinically relevant impact of INCS on neither ocular pressure, glaucoma, lens opacity nor cataract formation.

**Key words:** Intranasal steroids, Intraocular pressure, Glaucoma, Cataract, Chronic upper airway disease

## Introduction

The intranasal corticosteroids (INCS) are prescribed in the management of upper airway inflammation. With their well-known anti-inflammatory properties, they provide relief for rhinitis symptoms, decongest airway oedema, restore nasal breathing, decrease mucus production and reduce the recurrence rates of upper airway inflammation<sup>(1,4-6)</sup>. Therefore, INCS are recommended in many evidence-based guidelines, for the management of

upper airway disease<sup>(7,8)</sup>.

Adverse effects of intravenous, oral and inhaled steroids following systemic absorption are well established<sup>(1-3)</sup>. In recent years, the development of molecules designed to achieve potent, localized activity on nasal mucosa with minimal risk of systemic exposure. Patients are able to benefit from the therapeutic effects of the corticosteroids, while minimizing the use of steroid therapy via other routes<sup>(9)</sup>.

In recent years there have been an increasing number of case reports and case series frequently citing INCS as a contributing factor to ocular adverse effects, challenging their role as a safer option<sup>(10-12)</sup>. Although it has long been recognised that a high dose inhaled corticosteroids can lead to systemic adverse effects, including the risk of developing ocular hypertension or open-angle glaucoma<sup>(1, 13)</sup>, there has been little indication of such risk with intranasal administration. The ability of INCS to cause adverse systemic effects is mediated via nasal mucosa, or the gastrointestinal tract absorption. The newer generations of intranasal steroids are not only highly lipophilic, but also undergo rapid and extensive first-pass metabolism following ingestion; and therefore, have negligible systemic absorption from the latter route. Systemic bioavailability of drugs such as mometasone furoate or fluticasone propionate is as low as 0.1%, and less than 2%, respectively. This compares favorably to older generation of INCS, where one-third to half of an intranasal dose can reach the systemic circulation. Additionally, compared to inhaled corticosteroids, nasal steroids are usually administered in much smaller doses with more limited contribution to the systemic circulation<sup>(4, 9, 13, 14)</sup>. Hence, the systemic effect of INCS, and its adverse clinical impact remain controversial.

In recent years, there have been published case reports and series, reporting changes in intraocular pressure or lens opacity in those consuming INCS<sup>(11-13)</sup>. However, few higher-level studies are cited when discussing ocular effects from INCS. Narrative reviews have the potential for bias in their summaries when not systematic in the review of the literature. Therefore, the aim of this study is to systematically review the evidence of the effect of INCS on potential adverse ocular effects.

**Materials and methods**

A systematic review was performed to identify published manuscripts with original data on any ocular effects from the use of INCS. PRISMA guidelines<sup>(23)</sup> and recommendations from the Cochrane Handbook of Systematic reviews were followed where possible.

**Databases searched**

The electronic databases were used to conduct the search. Medline database was searched from 1946 to 21st of Nov 2013. Embase database was searched from 1974 to 22nd of Nov 2013. The bibliographies of studies subject to full-text analysis was reviewed and used as a further data source.

**Search strategy**

A search strategy was constructed using a combination of medical subject headings and keywords relevant to nasal and sinus disease as well as intranasal steroids. The search strategy used to search the electronic databases, Embase, and Medline databases

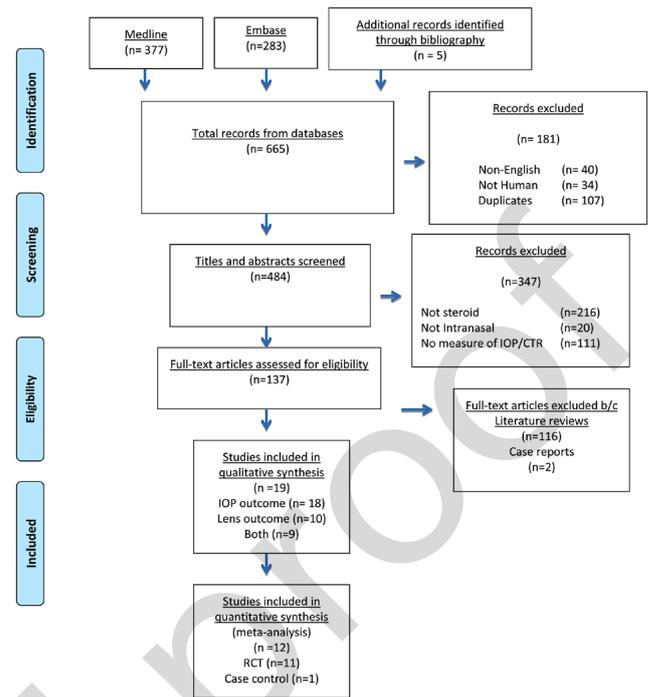


Figure1. PRISMA chart.

are shown in Table 1.

**Study selection**

Study selection was performed by two authors (NA and RJH) in an unblinded standardized manner. The following steps were taken. The identified publications from the electronic databases were combined. The lists of identified publications were scanned using PRISMA guidelines<sup>(15)</sup>, shown in Figure 1. Non-English, non-human studies, and duplicate publications were identified and removed.

The publications extracted were then further scanned using a combination of abstract or full-text. Those, which failed to use steroid as a treatment, apply it exclusively intranasal, nor reported original data of intraocular pressure or lens opacity were excluded.

The publications extracted were grouped by title review into studies that are case reports, literature reviews or comparative studies. The two former were excluded and the later was further included for qualitative synthesis.

**Criteria for included studies**

**Type of studies**

Any studies on population of patients using INCS were included. Randomized controlled trials (RCTs), cohorts, case-control and case series were caught. Simple case reports were not included.

### Types of participants

Adults and children with either, allergic rhinitis, (seasonal or perennial or moderate-severe persistent allergic rhinitis) confirmed by skin prick testing or in-vitro test for an allergen specific IgE or CRS as defined by either European Position Paper on Rhinosinusitis and Nasal polyps 2007<sup>(16)</sup>, or Rhinosinusitis Task Force Report<sup>(17)</sup> and its revision<sup>(18)</sup> were included.

### Types of interventions

Studies involving topical steroid therapies versus either placebo, no treatment or another topical steroid therapy were considered. Trials using any co-interventions of oral steroid, antihistamines, decongestants, antibiotics (topical or intravenous) were included when the co-interventions were equally applied in both groups.

### Outcome measures

All outcomes reporting changes or abnormality in IOP, visual acuity, cup to disc ratio, ocular hypertension, or the detection, and or alteration of known glaucoma were assessed. Additionally, any change relating to, cataract or measurements of lens opacity were also included.

### Exclusion criteria

Any study that did not report an outcome of IOP, glaucoma assessment, lens opacity or cataract assessment. Case reports only. An exogenous corticosteroid taken either topically, inhaled or orally when not applied equally between controls and INCS users.

### Risk of bias

Risk of bias in randomized controlled trials was assessed at a study level using the Cochrane Risk of Bias Assessment Tool<sup>(19)</sup>.

### Statistical analysis

Statistical analyses were performed using SPSS v 20.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Data was presented as descriptive statistics only. Parametric scale data was described with mean and standard deviation. Nonparametric data is described with median and interquartile range (IQR). Where, no IQR was provided, absolute range was recorded.

### Results

The search produced a total of 660 studies. The first-level screening removed 107 irrelevant studies or duplicates, 40 non-English, and 34 studies where the subjects were not human. The flowchart of the study selection using PRISMA flowchart<sup>(15)</sup> is provided in Figure 1. All 479 remaining abstracts were reviewed to assess if they met the inclusion criteria. An additional 5 studies were identified from bibliographic search from reviewed articles, bringing the total of the studies to 484 to be screen.

The title and abstract screen of the references identified 216 (44.6%) studies that did not use corticosteroids, 20 (4.1%) that either failed to apply the steroid intranasally or failed to avoid oral, inhaled or intravenous steroids as co-intervention, and 111 (23.0%) of the studies that failed to report original data on intraocular pressure, lens opacity or incidence of glaucoma or cataract. The full text analysis of the remaining 137 studies identified 116 (84.7%) studies that were literature reviews, and 2 (1.5%) case reports. Nineteen (n = 19) (13.9%) studies were included.

### Included studies

Of these 19 included studies, 9 reported data outcome on IOP<sup>(3, 6, 11, 13, 20-24)</sup>, 1 on lens opacity<sup>(25)</sup>, and 9 studies reported data on both IOP and lens opacity<sup>(14, 26-33)</sup>. This then left 18 (94.7%)<sup>(3, 6, 11, 13, 14, 20-33)</sup> studies on IOP, and 10 (55.6%)<sup>(14, 25-33)</sup> on lens opacity in clearly defined patient groups that could be used for comparison in this systematic review<sup>(14, 26-33)</sup>. The study characteristics of the 19 included manuscripts are described in Tables 4 and 5. Studies followed the standard practices. The diagnosis of glaucoma was either based on the degree of increase in IOP (>10mmHg or >20% from the baseline) or the measure of IOP alone (>20mmHg). The same process was followed in measuring the lens opacity, whereby the diagnosis was made by a qualified ophthalmologist in accordance to a rigid set of guidelines. This involved slit lamp examination and refractometer.

### Intraocular pressure and INCS

Of the 19 studies included in this review, 18 (94.7%) reported outcomes on IOP, but only 11 (63.2%)<sup>(1, 20-23, 26-31)</sup> had a control group. These studies included 10 RCTs (57.9%)<sup>(6, 20-23, 26-31)</sup> and one case-control study<sup>(1)</sup>.

Of the eleven RCTs, three (n = 3) assessed children aged between 2 to 11 years old<sup>(28-30)</sup>, three (n = 3) on children (>12 years old) and adults<sup>(26, 27, 31)</sup>, and four (n = 4) on adults between 18 to 65 years of age<sup>(20-23)</sup>. The case control study included both children and adults population<sup>(1)</sup>. Majority of the comparative studies were conducted on individuals with Seasonal (SAR) or Perennial (PAR) Allergic Rhinitis for at least 6 months and positive skin prick test, who were exclusively being treated with no other form of delivery method of steroids other than intranasal. One study<sup>(22)</sup> was conducted on postoperative FESS patients; and the case-control study<sup>(1, 3)</sup> was conducted on individuals with glaucoma and ocular hypertension who were also happen to be on intranasal corticosteroids. All studies except four (n = 4)<sup>(22, 23, 29, 30)</sup>. RCTs excluded individuals with glaucoma or ocular hypertension. The comparative studies included in this systematic review, together report on the effect of a variety of intranasal steroids including Fluticasone, Mometasone, Beclomethasone, Ciclesonide, and Budesonide. Almost all studies reported spe-

Table 1. Search strategy used for Medline. A similar strategy was used in Embase.

Population / Disease	Intervention	Outcome 1: IOP	Outcome: Lens Opacity
#1 Paranasal sinus disease explode all trees except from neoplasm (MeSH)	#18 Steroids explode all trees (MeSH)	#33 administration, topical Explode all trees (MeSH)	#39 Eye explode all trees for eye disease, eye abnormality, eye manifestations, eye pain, ocular hypertension glaucoma (MeSH)
#2 Sinusitis explode all trees (MeSH)	#19 Anti-inflammatory agents explode all trees (MeSH)	#34 administration, intranasal Explode all trees (MeSH)	#40 Eye disease Explode all trees (MeSH)
#3 Rhinitis explode all trees (MeSH)	#20 Anti-inflammatory agents, Non-steroidal explode all trees (MeSH)	#35 (spray* OR intranasal* OR intra-nasal OR nasal*)	#41 Glaucoma explode all trees (MeSH)
#4 (sinusitis* OR Rhinosinusiti* OR Nasosinusiti* OR Pansinusiti* OR Ethmoiditis OR Antritis OR Sphenoiditis)	#21 (19 NOT 20)	#36 stents OR Otorhinolaryngologic Surgical Procedures	#42 Intraocular pressure, Explode all trees (MeSH)
#5((sinus* OR sinonasal OR endonasal OR paranasal OR nose OR nasal OR rhinosinus*) AND (inflammation OR inflamed OR pain* OR ache OR aching OR infect* OR Pressure OR Purulen* OR obstruct* OR block* OR drainage OR discharge* OR symptom* OR disease*))	#22 Glucocorticoids	#37 (irrigation OR douche OR rinse OR drops OR "nasal lavage")	#43 Tonometry OR tonometry, ocular Explode all trees (MeSH)
#6 Explode respiratory hypersensitivity all trees (MeSH)	#23 (Steroid* OR Coritoid* OR Glucocorticoid* Or Corticosteroid*)	#38 (33 OR 34 OR 35 OR 36 OR 37)	#44 (intraocular* OR Ocular* OR intra-ocular pressure OR intraocular pressure OR IOP)
#7 heyfever* or hey fever	#24 (Betamethasone* OR Betametason OR Betadexame-thasone OR Flubenisolone)		#45 (tonometric* OR tonometer* OR tonomet* OR glaucomatous field OR Humphrey Perimeter OR perimetric effect
#8 pollinosis* OR Ozena* Or Allergic* OR Catarrh* Or Catarrhal* OR Rhinorrhoea* OR Coryza*	#25 (Hydrocortison* OR Cortisol OR Celesto*)		#46 (visual field OR Vision disorder OR visual field test)
#9 Respiratory tract infection OR common cold	#26 (Dexamethason* OR Hexadecardrol OR decadron OR dexasone OR hexadrol)		#47 (Optic neuropathy OR Optic disc OR hypertension OR ocular hypertention
#10 Explode nasal obstruction	#27 (Budesonid* OR Horacort OR Pulmicort OR Rhinocort OR methylfluorprednisone)		#48 (pilocarpine OR timolol OR beta-blockers OR iatanoprost OR brimonidine)
#11 Explode nasal polyps all trees (MeSH)	#28 (Flunisolid* OR nasalide* OR millicorten OR Oradexon)		#49 (Cyclophotocoagulation OR photocoagulation OR cylco-trabeculospasis OR Trabeculoplasty OR trabeculectomy OR laser coagulation OR laser therapy, eye OR lasers, eye OR semiconductor
#12 polyp*	#29 Fluticason* OR flonase OR flounce OR mometason* OR nasonex		#50 (39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49)
#13 Nose, explode all trees (MeSH)	#30 Triamcinolon* OR Nasacort OR tri next nasal OR aristocort OR volon		
#14 nose* OR nasi* OR intranasal* OR sinonasal* OR paranasal* OR endoscop* OR FESS	#31 Anti-asthma agents explode all (MeSH)		
#15 (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12)	#32 (18 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)		
#16 (#13 OR #14)			
#17 (#15 AND #16)			
			#51 Cataract Explode all trees (MeSH)
			#52 Capsule opacification OR Capsulorhexis OR Lens Crystalline OR Protein folding OR Protein aggregation OR Covalent protein damage
			#53 Visual acuity OR vision disorder OR vision, low OR blindness Or eye injury
			#54 Corneal topography OR Lens implantation OR Cataract extraction
			#55 eye OR ocular* OR visual OR vision OR intraocular* OR ophthal*
			#56 (51 OR 52 OR 53 OR 54)
			#57 (55 AND 56)
			Final
			#58 (50 OR 57)
			#59 (17 AND 32 AND 38 AND 58)

cific tools such as tonometry in addition to detailed physician examination in collecting the intraocular pressure measurements; and defined the measures considered abnormal prior to commencing the study. The outcomes were either reported as detailed measures of changes in IOP (continuous), and/or presence or absence of glaucoma (dichotomous).

The study outcomes for intraocular pressure and occurrence of

glaucoma are described in Table 4. A total of 4376 patients in 10 RCTs were assessed for the effect of INCS on IOP and occurrence of glaucoma. Four studies report data on adults, three on children, and three on patients above twelve years of age. The studies assess a range of INCS. The most commonly used INCS was Fluticasone at doses ranging from 55 to 110mcg per day. All studies, except one, compare the INCS group with a placebo group. All studies measured the outcome with tonometry or

Table 2. Characteristic of the included studies with investigations into intra-ocular pressure (IOP) or glaucoma incidence.

Author	yr	Design	n	Population	Intervention	Placebo (y/n)	Outcome measure	Type of data
				Type / daily dose/ Duration		Tool used to measure outcome/ Definition of abnormal		
Bross-Soriono	2004	RCT	360	18-60 yrs. All had Rhinitis No Ocular HT or Glaucoma No HT or DM	Fluticasone 200mcg Mometasone 200mcg Beclomethasone 400mcg 365 days	Y	Tool: Tonometry & physician reported Abnormal: IOP >22 mmHg	Continuous (mmHg)
Ranter	2006	RCT	703	18-65 yrs. >2 yrs SAR, +ve SPT or specific IgE, No Glaucoma or Cataract, No other forms of Steroid	Ciclesonide 25 to 200mcg 14 days	Y	Tool: Tonometry Abnormal: IOP > 20mmHg	Dichotomous
Chervinsky	2007	RCT	474	>12 yrs. >2 yrs PAR, +ve ≥ 1 allergy test, No Glaucoma or Cataract	Ciclesonide 200mcg 365 days	Y	Tool: Tonometry Abnormal: IOP ≥ 25mmHg	Dichotomous
Rosenblut	2007	RCT	592	≥ 12 yrs. ≥2 yrs. PAR +ve SPT No Glaucoma or Cataract	Fluticasone 110mcg 365 days	Y	Tool: Tonometry Abnormal: IOP ≥21mmHg	Dichotomous
Maspero	2008	RCT	492	2-11 yrs. >6mths PAR All asymptomatic +ve SPT w/in 12mths before start No glaucoma or Cataract	Fluticasone 110 mcg Fluticasone 55 mcg 84 days	Y	Tool: Physician & Tonometry Abnormal: Not defined	Dichotomous
Meltzer	2009	RCT	948	2-11 yrs., 3 phase study: SAR 2 wks. HPA axis safety 6 wks. PAR 12 wks.	Fluticasone 55mcg Fluticasone 110mcg 14-84 days	Y	Tool: Physician report Abnormal: Not defined	Dichotomous
Ranter	2009	RCT	225	6-11 yrs. >1 yr. PAR +ve SPT No other forms of steroid	Mometasone 100mcg OR Beclomethasone 168mcg 365 days	N	Tool: Tonometry Abnormal: Not defined	Continuous (mmHg)
Rotenberg	2011	RCT	60	>18 yrs., All post FESS No other forms of steroids Non-smokers	Budesonide Spray - 256mcg daily Irrigation - 0.5mg/mls BD (1000mcg daily) 182-365 days	Y	Tool: Tonometry Abnormal: Not defined	Continuous (mean)

Table 2. Continued.

Yuen	2013	RCT	19	18-85 yrs., All had controlled OHT or mild POAG, No steroid > 6mths prior start	Beclomethasone 14-42days	400mcg	Y	Tool: Tonometry Abnormal: >20% IOP change in >2 visits	Dichotomous
LaForce	2013	RCT	303	≥12 yrs., ≥2yr PAR, +ve SPT No Glaucoma or Cataract	FFNS 730 days	110mcg	Y	Tool: Tonometry Abnormal: IOP ≥ 10mmHg from baseline	Dichotomous
Garbe	1997	Case control	9793 cases / 38325 controls	Adults Patients identified from prescription claims data in the database (medications for either treatment of Glaucoma or OHT for > 1 yr. Controls from those enrolled for 1yr w/out diagnosis of glaucoma or receiving tmt for such condition Exposure for ≥ 3mths prior index date	1. High exposure group: Fluticasone / Flunisolide OR Beclomethasone / Budesonide / Triamcinolone 2. Medium to Low Exposure group: Doses below the above 14 days	200mcg	N/A	Tool: Physician reported Abnormal: Not defined	Dichotomous
Seiberling	2013	Case series	18	18-70 yrs. Failed conventional treatment CRS/WNP or recurrent nasal polyps No Glaucoma or Cataract	Budesonide 28 days	500 mcg	N/A	Tool: Tonometry Abnormal: IOP ≥ 20mmHg	Dichotomous
Forwith	2011	Case series	50	Adults scheduled for FESS, CRS >8mths, CT sinuses completed	Sinus Stent Mometasone 30 days	370mcg	N/A	Tool: Tonometry Abnormal: Not defined	Continuous (mean)
Ozkaya	2011	Case series	150	7-15 yrs., >2yrs PAR, +ve skin test, >3 visits to OPC for 3 yrs., No other forms of steroids	Budesonide 730 days	500mcg	N/A	Tool: Tonometry Abnormal: Not defined	Continuous
Spilliotopoulos	2007	Case series	54	22-25 yrs., All allergic rhinitis, No other steroids, Otherwise healthy	Tramazoline Dex: 35 days	240mcg 40mcg	N/A	Tool: Tonometry Abnormal: IOP + 4 mmHg or >normal	Continuous
Bui	2005	Case series	12	Adults All had OHT or glaucoma	Fluticasone Budesonide Mometasone Triamcinolone Doses not specified 480 days		N/A	Tool: Tonometry Abnormal: Not defined	Continuous

Table 2. Continued.

Author	yr	Case series	n	Population	Intervention	Placebo (y/n)	Outcome measure	Type of data
Ozturk	1998	Case series	26	Adults Post FESS, NS>3 mths	Budesonide / Beclomethasone 200mcg 90-570 days	N/A	Tool: Tonometry Abnormal: IOP>21mmHg	Dichotomous
Opatowsky	1995	Case series	3	Identified cases when they showed elevation of IOP with steroids	Beclomethasone Dose not specified 30 days	N/A	Tool: Tonometry Abnormal: Not defined	Continuous

IOP: Intraocular pressure; DM: Diabetes; HT: Hypertension; PAR: Perennial Allergic Rhinitis; SPT: Skin prick test; SAR: Seasonal Allergic Rhinitis; +ve: Positive; CRS: Chronic Rhinosinusitis; OPC: outpatient clinic; FESS: Functional Endoscopic Sinus Surgery; INS: Intranasal Corticosteroid; HPA: Hypothalamus-pituitary-adrenal; POAG: Primary open-angle glaucoma; CRSwNP: Chronic Rhinosinusitis with Nasal polyps

Table 3. Characteristic of the included studies investigating lens opacity (LO) or the formation of cataracts.

Author	yr	Design	n	Population	Intervention	Placebo (y/n)	Outcome measure	Type of data
Chervinsky	2007	RCT	474	>12 yrs., >2 yrs. PAR, +ve ≥ 1 allergy test, No Glaucoma or Cataract	Ciclesonide 200mcg 365 days	Y	Tool: Slit lamp & LOCS II Abnormal: Not defined	Dichotomous
Rosenblut	2007	RCT	592	≥ 12 yrs. ≥2 yrs. PAR +ve SPT No Glaucoma or Cataract	Fluticasone 110mcg 365 days	Y	Tool: Slit lamp examination Abnormal: Not defined	Continuous
Maspero	2008	RCT	492	2-11 yrs. >6mths PAR (all symptomatic) +ve SPT w/in 12mths before start No Glaucoma or Cataract	Fluticasone 110 mcg OR 55 mcg 84 days	Y	Tool: Physician & Refractometer Abnormal: Not defined	Dichotomous
Meltzer	2009	RCT	948	2-11 yrs. 3 phase study: - SAR 2 wks. - HPA axis safety 6 wks. - PAR 12 wks.	Fluticasone 55 mcg OR 110mcg 14-84 days	Y	Tool: Physician report Abnormal: Not defined	Dichotomous
Ranter	2009	RCT	225	6-11 yrs. >1 yrs. PAR +ve SPT No other forms of steroid	Mometasone Beclomethasone 365 days	N	Tool: Slit lamp Abnormal: Not defined	Dichotomous
LaForce	2013	RCT	303	≥12 yrs., ≥2yr PAR, +ve SPT No Glaucoma or Cataract	FFNS 730 days	Y	Tool: LOCS III Abnormal: Visual acuity ≥0.18 Or Disc:Cup ratio ≥ 66%	Dichotomous

Table 3. Continued.

Author	yr	Case series	50	Adults scheduled for FESS, CRS >8mths All had CT sinuses	Sinus Stent Mometasone 30 days	370mcg	N/A	Tool: Slit lamp & LOCS III Abnormal: Not defined	Dichotomous
Ozkaya	2011	Case series	150	7-15 yrs., >2yrs PAR, +ve skin test, >3 visits to OPC for 3 yrs. No other forms of steroids	Budesonide 730 days	500mcg	N/A	Tool: Autokerato-refractometer Abnormal: Central corneal dioptric power >47.20	Continuous
Ozturk	1998	Case series	26	Adults; Post FESS, INS>3 mths, No Cataract	Budesonide/Beclomethasone 200mcg 90-570 days			Tool: Physician report Abnormal: Not defined	Dichotomous
Derby	2000	Case series	217	<70 yrs. From a GP research database, No other form of steroids	Beclomethasone (140 patients) & other types Dose not specified			Tool: Physician report Abnormal: Not defined	Continuous

PAR: Perennial Allergic Rhinitis; SPT: Skin prick test; SAR: Seasonal Allergic Rhinitis; +ve: Positive; CRS: Chronic Rhinosinusitis; OPC: outpatient clinic; FESS: Functional Endoscopic Sinus Surgery; INS: Intranasal Corticosteroid

Table 4. Results from included studies with investigations into intra-ocular pressure (IOP) or glaucoma incidence.

Author	yr	Total (n)	Con-tols (n)	Glaucoma or raised IOP in non- INCS group (n)	INCS group (n)	Glaucoma or raised IOP in INCS group (n)	Difference between INCS & non-INCS group
Bross-Soriano	2004	360	90	0	90 on Fluticasone 200mcg/d 90 on Mometasone 200mcg/d 90 on Beclomethasone 400mcg/d	0 Mean IOP: FFN: 15.7 mmHg (R) + 15.8 mmHg (L) MMF: 16.7 mmHg (R) + 16.8 mmHg (L) Beci: 16.3 mmHg (R) + 16.3 mmHg (L)	No significant difference
Ranter	2006	703	148	3	578 on Ciclesonide: - 146: 25mcg/day - 143: 50mcg/day - 145: 100mcg/day - 144: 200mcg/day	8	No significant difference
Chervinsky	2007	663	222	0	441	0	No significant change Mean difference: -0.1(-0.5-0.3 95% CI)
Rosenblut	2007	592	144	0	448	0	No significant difference Mean change in IOP: Wk12: -0.2 Wk 24: -0.1 Wk 52: 0.1 (L eye) & 0.2 (R eye)

Table 4. Continued.

Maspero	2008	492	162	0	169 on 110 mcg/day FFN 163 on 55 mcg/day FFN	0	No significant difference
Meltzer	2009	948	330	0	618 - 297: 55 mcg FFN - 321: 110mcg FFN	0	No significant change
Ranter	2009	232	0	No placebo Compares MFN group with BDP group	153 on Mometasone 79 on Beclomethasone	0 in MFN group Baseline: 10-22 (R) & 10-21 (L) Endpoint: 9-21 (R) & 9-22 (L)  1 in Beclomethasone group: Baseline: 18/18mmHg After 1yr.: 5/26mmHg	
Rotenberg	2011	64	22	0	21 in Spray group 21 in Irrigation group	0 in Spray group: Baseline IOP: 12.9±3.1 1 yr. IOP: 13.4±2.1  0 in irrigation group: Baseline IOP: 13.5±2.4 1 yr. IOP: 12.9±2.6	No significant change
Yuen	2013	19	10	3	9	3  Baseline IOP: 15.8±4.58 6wks IOP: 16.3±4.8	No significant change
LaForce	2013	303	104	199	199	Time to first occurrence of an IOP event: <1%  Mean change from baseline: -1.0 to -0.3 and IOP returned to normal within 2mmHg from baseline at wk. 104	No significant change
Garbe	1997	48118	38325	Non-glaucoma cases	21 (0.2%)	Any INCS: OR 1.09 (0.87-1.37)  Continuous INCS: OR 1.02 (0.59-1.77)	No significant change  No observed elevated risk of ocular HT or open-angle glaucoma even after high-dose use of INCS

IOP: intraocular pressure; MMF: Mometasone; FFN: Fluticasone; BDP: Beclomethasone; INCS: intranasal corticosteroids; OR: Odds ratio; HT: Hypertension; wks.: weeks;

Table 5. Results of the included studies investigating lens opacity (LO) or the formation of cataracts.

Author	yr	n	Non-INCS group (n)	Cataract or increase in lens opacity in non-INCS (n)	INCS group (n)	Cataract or increase in lens opacity in INCS group (n)	Difference between the INCS & non-INCS group
Chervinsky	2007	474	165	<1%	331	<1%	No Significant difference
Rosenblut	2007	592	144	1 (0.50%) (PSC)	448	2 (0.33%) (PSC)	No Significant difference
Maspero	2008	492	162	2 (PSC)	169: 110mcg/day FFN Group A 163: 55mcg/day FFN Group B	0 in group A 1 in group B	No Significant difference
Meltzer	2009	948	330	2	618 - 297: 55mcg FFN - 321: 110mcg FFN	0	No Significant difference
Ranter	2009	205	68: BDP (no placebo, Compares two groups on INCS)	1	137: MFN Compares two groups on INCS – no placebo)	0	No Significant difference
LaForce	2013	303	104	0	199	0	No Significant difference

PSC: Posterior subcapsular cataract

Table 6. Outcome of case reports and case series - intraocular pressure or lens opacity.

Author	yr	Type	Population (n)	Focus	Outcome	Conclusion
Opatowsky	1995	Case series	3	IOP	1 Cataract 2 IOP increase	INCS increase IOP and risk of cataract
Bui	2005	Case series	12	IOP	Mean change detected But significance not measured	INCS can contribute to increase in IOP
Perdis	2010	Case report	1	IOP	Withdrawal from steroid, reduced IOP	Withdrawal from INCS reduces IOP
Lui	2011	Case report	1	CTR	Cataract	INCS increase risk of cataract

objective standard tools by a physician trained to examine the eye. The selected abnormal measures for IOP range from >21 to >25mmHg. Almost all outcomes reported were dichotomous. And all studies, including the studies that did not exclude patient with pre existing intraocular hypertension or glaucoma (3, 22, 23, 29, 30), reported no significant additional increase in IOP or occurrence of glaucoma in the INCS arm.

### Lens opacity and INCS

Ten out of the 19 (52.6%) (14, 25-33) studies included for qualitative analysis reported outcome on lens opacity, but only 6 (31.6%) (26-31) studies were randomised control studies. In contrast to the studies reporting on IOP, all studies included children in their selected population. Three studies included patients above twelve years of age (26, 27, 31), and three (n = 3) included children between the ages of two to eleven (28-30). In all studies, the patient population suffered from PAR or SAR for at least 6 months and had a

positive skin prick test. All studies excluded patients with known glaucoma or cataract. The studies were conducted for minimum of 6 weeks to a maximum of 2 years. In contrast to the studies on IOP outcomes, studies on lens opacity were limited to assessing the effects of Fluticasone or Ciclesonide and their relation to presence of cataract (in particular subcapsular cataract).

The outcomes for changes in lens opacity and occurrence of cataract are described in Table 5. The table demonstrates a total of 3014 patients in 6 RCTs. Half of the studies reported exclusively on children, and the other half on both adults and children above the age of twelve years. All patients were diagnosed with PAR for at least six months, and had at least one positive skin prick test. The most commonly tested INCS was Fluticasone at doses of 55 to 110 mcg per day. The patients underwent slit lamp examination by an ophthalmologist. All outcomes except in one study were dichotomous. Two studies reported the same

Table 7. Risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (Performance bias & detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (reporting bias)	Other bias
Bross-Soriano 2004	Green	Green	Yellow	Red	Green	Yellow
Ranter 2006	Yellow	Green	Yellow	Green	Green	Green
Chervinsky 2007	Green	Green	Yellow	Green	Green	Yellow
Rosenblut 2007	Yellow	Green	Yellow	Green	Green	Red
Maspero 2008	Green	Green	Yellow	Green	Green	Red
Meltzer 2009	Green	Green	Yellow	Red	Yellow	Red
Ranter 2009	Yellow	Green	Green	Green	Green	Red
Rotenberg 2011	Green	Yellow	Green	Green	Green	Green
Yuen 2013	Yellow	Green	Yellow	Green	Green	Yellow
LaForce 2013	Green	Green	Yellow	Green	Green	Red

green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias

rate of cataract detected in the placebo group; while all other studies reported zero outcomes for cataract in the INCS groups.

### Risk of bias

Comprehensive reporting of study methodology was inconsistent amongst randomised control trials (RCTs) (Table 7). Sequence generation randomization was reported but detail of sequence generation given in 50%<sup>(20, 21, 23, 27, 30)</sup>. All studies reported blind evaluators but only two reported details of methods implemented to ensure blinding<sup>(22, 30)</sup>. One study was open to patients<sup>(30)</sup>, however this study attempted to exclude patient bias by assessing evaluator outcomes only. All studies except one<sup>(22)</sup>, reported on concealment and allocation. Complete outcome data was reported in all but one<sup>(29)</sup>. Two studies<sup>(20, 29)</sup> failed to report outcome data on withdrawals. Half of the studies were sponsored by pharmaceutical companies<sup>(27-31)</sup> with remaining studies did not report any conflict of interest.

### Discussion

The changes in lens opacity and ocular hypertension from corticosteroids, administered orally, intravenous and, to a lesser degree, inhaled, are well documented. Prolonged exposure to the corticosteroids via any of these routes can result in intra-ocular pressure related visual loss or cataract<sup>(12, 25, 29, 33, 34)</sup>. The adverse profile of the corticosteroids, results largely from systemic absorption of the drug regardless of delivery type<sup>(4)</sup>.

However, the occurrence of similar adverse events from intranasal delivery of the steroids remains controversial<sup>(12, 25, 33)</sup>. The literature is replete with non-systematic reviews on the subject (n = 116) with 42% (n = 8) of all original study representing case

series only. In recent years, a rising trend of case reports and narrative literature reviews warn of the potential of INCS to cause ocular hypertension, worsening of preexisting glaucoma and changes in lens opacity, however, few offer more than level 4/5 data to support their recommendations. Such comments and case series/report data can lead to an environment of fear and subsequent poor prescribing patterns of intranasal steroids by primary care physicians<sup>(10-13, 29, 36)</sup>.

The established success of INCS in treatment of upper airway inflammatory disease has led to increased long term prescribing patterns by specialists and recommendations for long-term use (16, 18). The intranasal formulations are designed to allow direct local delivery of the drug to the target area, whilst minimizing the risk of systemic absorption<sup>(4, 29)</sup>. The latest generation of INCS, such as Fluticasone propionate, Mometasone furoate, Ciclesonide, and Fluticasone furoate come close to the ideal INCS, in terms of the pharmacokinetic or pharmacodynamics properties. They have a high degree of glucocorticoid receptor affinity, potency and specificity; as well as low systemic bioavailability, high rate of hepatic first-pass metabolism and therefore rapid systemic elimination. Moreover, the slow-release drug-lipid complexes allow clinically desirable outcome with once-daily dosing<sup>(9, 37)</sup>. This is all, in addition to remaining very successful in achieving the clinical efficiency by reducing mucosal swelling, improving sinus drainage and therefore hastening elimination of pathogens, and inhibiting the release and formation of mucous secretagogues<sup>(4, 5, 25, 33)</sup>.

In 1960, Black et al.<sup>(38)</sup>, first described the association between systemic corticosteroids and the development of posterior

subcapsular cataract in patients with rheumatoid disease. Later reports such as Kewlery et al. (39), and Cumming et al. (40), confirmed similar association with the use of inhaled corticosteroids. However, intranasal steroids do vary significantly in their systemic absorption, bioavailability, and lipophilicity, to the corticosteroids administered via other routes (4). With intranasal delivery, up to 30% of the dose is deposited and remain in the nose depending on the drug's lipophilicity; the remainder is swallowed. Ninety-nine percent of the swallowed INCS is subject to the first-pass metabolism in the liver for second-generation agents. Hence, the systemic side effect from INCS depends on not only the lipophilicity of the administered corticosteroid and direct absorption via the nasal mucosa, but also its systemic and local bioavailability, and hepatic first-pass metabolism (4, 9, 13, 25, 36, 37). Whereas, inhaled corticosteroids, which have been linked to systemic adverse events, are primarily absorbed through the respiratory mucosa of the lower airway. And although, oropharyngeal deposition may occur, only a fraction is swallowed and undergoes hepatic first-pass metabolism. The remainder is absorbed systemically (9, 37, 41). Doses used in the lower airway are traditionally much larger than those used intranasally.

Fraunfelder et al. (36), argues that nasal steroids can reach ocular structures in levels sufficient to cause ocular hypertension and posterior subcapsular cataract in susceptible patients. This study had identified 21 patients who had PSC following administration of nasal or inhaled Beclomethasone. Most of the patients were on the medication for more than five years and often in higher than recommended dose of 252 mcg/day. Most importantly, 9 out of 21 patients were also using systemic steroids concomitantly. The concomitant use of systemic steroids in a large number of the patients, in these studies, is a significant confounding factor. Eight years later, Ozturk et al. (14), demonstrated a lack of any considerable change in the lens opacity of all patients studied, despite using higher dose of nasal Beclomethasone (400 mcg/day) for over 19 months.

This systematic review found no difference in intraocular pressure or diagnosis of glaucoma in 4376 patients across 10 randomised control trials (20-23, 26-31), exposed to a range of intranasal steroids (including new and old generation INCS) from 2-104 weeks, between controls and INCS users. Therefore, level one evidence supports a low risk for INCS use in the management of upper airway inflammatory disease. With a varying duration of INCS from 2 weeks to 2 years, IOP changes can occur within these time frames. IOP changes can be seen within hours after a parenteral dose of corticosteroid (42) and current recommenda-

tions within the ophthalmic literature suggests a 2 week review of IOP when patients commence non-parenteral exogenous corticosteroid use (43). There were 5 studies that included patients with glaucoma or ocular hypertension in their analysis. Four of these studies were RCTs (22, 23, 29, 30) and one case control (1). All five studies concluded that INCS does not worsen existing ocular hypertension or glaucoma.

This review also found that there was no difference in lens opacification or the new diagnosis of cataracts between INCS users and control group in 3014 patients across 6 randomised control trials (26-31), following exposure to Ciclesonide or Fluticasone for 6 to 104 weeks. Therefore, level one evidence supports INCS as a safe treatment of upper airway inflammatory disease, and does not appreciably increase the risk of cataract in patients exposed to this medication for a considerably long period of time.

Meta-analysis of the data was not possible, as almost all studies reviewed in this systematic review, reported zero adverse ocular outcomes. This is an obvious limitation of our study as the zero adverse effects can either represent the absence of a true effect or an underpowered study, however the risk is likely to be very small.

## Conclusion

Data from studies with low levels of bias, do not demonstrate a clinically relevant impact of INCS on neither ocular pressure, glaucoma, lens opacity nor cataract formation. Level 1 studies report that INCS can be used without fear of ocular side effects resulting from INCS therapy. And even, in the presence of pre-existing ocular hypertension, level one data suggests negligible impact from INCS therapy.

## Acknowledgement

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## Authorship contribution

NA: Data collection, analysis and manuscript production; KS: Data collection and analysis. LK: Manuscript review and data analysis; RS: Design and expert manuscript review; KT: Manuscript review and preparation; GW: Manuscript review and preparation; RH: Design, analysis and manuscript review.

## Conflict of Interest

The authors declare no conflict of interest.

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