

REVIEW ARTICLE

Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis

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Abstract

Given the relationship between allergic rhinitis (AR) and asthma, it can be hypothesized that reducing inflammation in the upper airway with intranasal corticosteroid (INCS) medications may improve asthma outcomes. The goal of this study was to perform a systematic review with meta-analysis of the efficacy of INCS medications on asthma outcomes in patients with AR and asthma. Asthma-specific outcomes from randomized, controlled studies evaluating INCS medications in patients with AR were evaluated, including studies that compared INCS sprays to placebo, INCS sprays plus orally inhaled corticosteroids to orally inhaled corticosteroids alone, and nasally inhaled corticosteroids to placebo. Sufficient data for meta-analysis were retrieved for 18 trials with a total of 2162 patients. Asthma outcomes included pulmonary function, bronchial reactivity, asthma symptom scores, asthma-specific quality of life, and rescue medication use. The subgroup of studies comparing INCS spray to placebo had significant improvements in FEV1 (SMD = 0.31; 95% CI, 0.04–0.58), bronchial challenge (SMD = 0.46; 95% CI, 0.12–0.79), asthma symptom scores (SMD = –0.42; 95% CI, –0.53 to –0.30), and rescue medication use (SMD = –0.29; 95% CI, –0.58 to –0.01). Nasal inhalation of corticosteroids significantly improved morning and evening peak expiratory flow. There were no significant changes in asthma outcomes with the addition of INCS spray to orally inhaled corticosteroids. Thus, the results of this meta-analysis demonstrated that intranasal corticosteroid medications significantly improve some asthma-specific outcome measures in patients suffering from both AR and asthma. This effect was most pronounced with INCS sprays when patients were not on orally inhaled corticosteroids, or when corticosteroid medications were inhaled through the nose into the lungs. Overall, intranasal corticosteroid medications improve some asthma-specific outcome measures in patients with both AR and asthma. Further research is needed to clarify the role of INCS sprays as asthma-specific therapy, as well as the role of the nasal inhalation technique as a monotherapy in patients suffering from both asthma and AR.

Allergic rhinitis (AR) and asthma are highly prevalent and often comorbid diseases (1–3). Estimates indicate that approximately 10–30% of the general population has AR and the prevalence appears to be increasing worldwide (4, 5). Similar global trends have been found for the prevalence of asthma, with the greatest increases seen in developing countries as they become urbanized (4, 6–8). An epidemiologic association between AR and asthma has been consistently demonstrated across patient populations, including children and adults.

Estimates vary based on the rigor with which AR and asthma are diagnosed, but up to 80% of asthmatics are affected by AR, and conversely, up to 40% of patients with AR have concomitant asthma (9–13).

Aside from an epidemiological association, there is also evidence to support the idea of a ‘unified airway’ – the concept that the upper and lower airways function as a single unit and disease processes may be interrelated. Although this relationship needs further elucidation, the

literature supports a link between AR and asthma that is present at the anatomic, physiologic, pathologic, and therapeutic levels (14). Prior studies have shown that AR may complicate asthma management and lead to poor asthma control and outcomes (9). Patients with asthma and concomitant AR also have higher rates of primary care visits, hospitalizations, and emergency room visits than those with only asthma (9, 15–18). Additionally, some studies have shown that treatment for AR in asthmatics can reduce healthcare costs and lead to better asthma control (19, 20).

Given the relationship between AR and asthma, it can be hypothesized that reducing inflammation in the upper airway with intranasal corticosteroid (INCS) medications may improve asthma outcomes. As a group, INCS medications include INCS sprays that deliver medication primarily to the nasal mucosa and nasally inhaled corticosteroids that deliver medication to both nasal and lower airway respiratory epithelium. Although many studies have explored this question, conclusions from individual studies have been conflicting, with some studies indicating INCS medications improve asthma outcomes, while others have shown no benefit (21, 22). The 2010 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommended management of AR with INCS medications, but did not find enough evidence to indicate a clear clinical benefit from the use of INCS sprays for asthma (23). Since the 2010 ARIA revisions, several new studies have been published specifically addressing the use of INCS medications in asthmatics with AR. The objective of this study was to perform an updated systematic review with meta-analysis assessing the impact of INCS medications upon asthma outcomes in patients with AR and comorbid asthma. This review includes three additional subgroup analyses: INCS sprays alone *vs* no treatment, INCS sprays plus asthma-specific medication *vs* asthma-specific medication alone, and nasally inhaled corticosteroids alone *vs* no treatment.

Methods

Search methods

Two authors independently performed the literature search utilizing prespecified inclusion/exclusion criteria. The PubMed (1950 to May 2012) and Cochrane Library (May 2012) databases were searched using the following keyword: [rhinitis AND asthma AND nasal steroids]. The MEDLINE database (January 1966 to May 2012) was searched using the following MESH terms: [(rhinitis or allergic rhinitis or (rhinitis, allergic, perennial) or (rhinitis, allergic, seasonal)) AND (asthma or wheeze) AND (nasal or nasal mucosa or administration, intranasal or topical) AND (corticosteroid or glucocorticoids or beclomethasone or anti-inflammatory agents)]. The reference lists of all obtained articles were examined for additional studies, and authors of published guidelines, experts in the field, and study sponsors were contacted for additional studies. All articles were considered regardless of language.

Inclusion/exclusion criteria

Randomized controlled trials (RCTs) evaluating the efficacy of INCS medications on adults or children were included if they assessed at least one asthma-specific clinical outcome measure, to include pulmonary function, bronchial reactivity, asthma symptom scores, asthma-specific quality of life, or use of rescue medications. Single and double-blind studies were both included, as were appropriate crossover trials. Included studies had to specify clear diagnostic criteria for AR and asthma. The diagnosis of AR was established based on typical symptoms plus a positive skin prick test or serum-specific IgE to at least one inhalant allergen. Diagnosis of asthma was established by clinical symptoms and physiologic features, the Global Initiative for Asthma (GINA) criteria, or the American Thoracic Society (ATS) criteria. The following interventions were considered for inclusion: INCS spray *vs* placebo, INCS spray plus asthma-specific medications *vs* placebo nasal spray plus asthma-specific medications and nasally inhaled corticosteroid *vs* placebo. Standard asthma medications could include short and long acting beta-agonists, orally inhaled corticosteroids, systemic corticosteroids (oral or parenteral), leukotriene receptor antagonists, 5-lipoxygenase inhibitors, ipratropium bromide, sodium cromoglycate, and theophylline. To isolate the impact of nasal therapies, studies were included only if asthma medications remained constant throughout the study and the only variable that changed was the nasal therapy. Studies were excluded from the present analysis if they assessed the efficacy of two or more treatments simultaneously, had a wash-out period <1 week between treatments, or did not have a placebo control group. Any differences in opinion regarding the inclusion of certain studies in the review were resolved by discussion until unanimity was reached among all authors.

Data extraction and analysis

Data from included studies were extracted using standardized forms and checked by a second author. Each asthma outcome was assessed, and the results recorded as absolute values and/or changes from baseline, using the last time-point available for each study (unless noted otherwise). Data reported only in graphical plots were not extracted for pooled meta-analysis unless specific numeral points were discernible or the authors of the relevant studies were able to verify the data. In the event of missing or incomplete data, attempts were made to request further details of the published results from the authors directly.

The reported outcomes were analyzed as either continuous or dichotomous variables using REVIEW MANAGER v5.1 (Copenhagen, Denmark). For all dichotomous outcomes, the relative risk (RR) and an associated 95% confidence interval were calculated. For continuous data, the weighted mean difference (WMD) was determined for studies reporting outcomes on the same unit scale and the standardized mean difference (SMD) utilized when scales differed, along with 95% confidence intervals (CI). DerSimonian and Laird ran-

dom-effects models were utilized given suspected differences in intervention effect across studies. For outcomes combining dichotomous and continuous variables, generic inverse variance analyses were conducted to calculate standardized mean differences within a 95% confidence interval. Heterogeneity across study effects was assessed using chi-square test and the I^2 statistic. When possible, sensitivity analyses were conducted for all outcomes examining INCS spray vs placebo, INCS spray plus asthma-specific medications vs placebo nasal spray plus asthma-specific medications, or nasally inhaled corticosteroid vs placebo. Risk of bias for each study was evaluated using the Cochrane 'Risk of bias' tool, including selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting) (24).

Results

Included studies

The literature search identified a total of 23 trials assessing the efficacy of INCS medications in patients with allergic rhinitis and asthma (25–47). Of the 23 trials, adequate data for analysis were retrieved for 18 studies, including 14 parallel (30–40, 42, 43, 45) and four cross-over randomized, placebo-controlled trials (41, 44, 46, 47) (Table 1). The search strategy with flow diagram is presented per the PRISMA guidelines (Fig. 1) (48). Study design, type and dosing of intranasal corticosteroids, technique of administration, and outcome metrics varied between studies. Studies included a total of 2162 patients, of which 1659 completed the full study and 503 withdrew or dropped out. Three of the 18 studies contributed the largest population of participants: 509 patients from Nathan et al. (45), 366 patients from Katial et al. (43),

Table 1 Characteristics of included studies

Study	N	Participants	Active intervention*	Duration	Outcome
Agondi 2008	30	Mixed	1. BDP nasal spray	125 days	FEV1, PC20, symptoms, rescue medication use
Baiardini 2001	51	Adults	1. MMF nasal spray	4 weeks	QoL, rescue medication use
Corren 1992	18	Adults	1. BDP nasal spray	7 weeks	FEV1, PEF, PC20, symptoms
Dahl 2005	236	Mixed	1. FP nasal spray2. FP nasal spray, orally inhaled FP	6 weeks	PEF
Henriksen 1984	36	Children	1. BDP nasal spray	4 weeks	FEV1, PEF, symptoms
Katial 2010	366	Adults	1. FP nasal spray, orally inhaled FP/salmeterol	4 weeks	FEV1, PEF, symptoms, rescue medication use
Kersten 2012	25	Children	1. FF nasal spray	22 ± 3 days	FEV1, QoL
Nair 2010	25	Adults	1. FP nasal spray, orally inhaled FP 2. Placebo nasal spray, orally inhaled FP	12 weeks	FEV1, PEF, PC20, QoL
Nathan 2005	509	Adults	1. FP nasal spray	4 weeks	PEF, symptoms, rescue medication use
Pedersen 1990	30	Adults	1. Nasally inhaled budesonide	2 weeks	PEF, rescue medication use
Pedersen 1998	24	Children	1. Nasally inhaled budesonide	1 week	PEF, symptoms, rescue medication use
Pedroletti 2008	40	Children	1. MMF nasal spray	4 weeks	Rescue medication use
Reed 1998	74	Mixed	1. Flunisolide nasal spray 2. Beclomethasone nasal spray	4 weeks	Rescue medication use
Sandrini 2003	16	Adults	1. TA nasal spray	4 weeks	FEV1, PC20, symptoms
Scichilone 2010	17	Adults	1. Budesonide nasal spray	2 weeks	FEV1, QoL
Stelmach 2005	54	Adults	1. BDP nasal spray; placebo inhaler 2. BDP nasal spray; orally inhaled BDP 3. Placebo nasal spray; placebo inhaler 4. Placebo nasal spray; orally inhaled BDP	16 weeks	FEV1, PC20, symptoms, rescue medication use
Thio 2000	93	Adults	1. FP nasal spray 2. FP nasal spray 3. BDP nasal spray	6 weeks	FEV1, PC20
Watson 1993	42	Children	1. BDP nasal spray	4 weeks	PC20, symptoms

BDP, beclomethasone dipropionate; MMF, mometasone furoate; FP, fluticasone propionate; FF, fluticasone furoate; TA, triamcinolone acetonide; FEV1, forced expiratory volume in 1 s (liters); PC20, histamine or methacholine dose provoking a 20% decrease in forced expiratory volume in 1 s; PEF, peak expiratory flow (l/min); symptoms, severity and/or frequency of asthma symptoms; QoL, asthma-related quality of life.

*All studies included one control arm with administration of a placebo nasal spray unless noted otherwise.

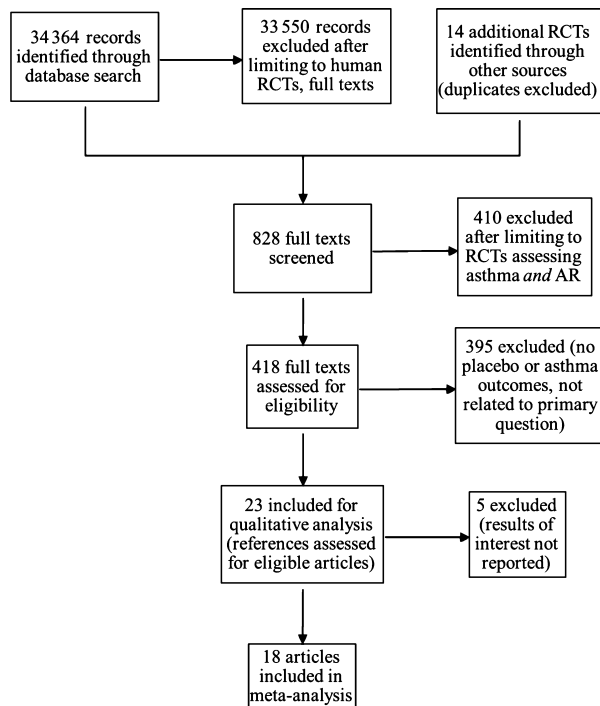


Figure 1 PRISMA search strategy.

and 236 patients from Dahl et al. (33). The remaining trials enrolled smaller numbers of patients ranging from 16 to 90. Ten studies assessed primarily adult populations, five only recruited pediatric participants, and three studies enrolled both adults and children into the trials. Twelve of the 18 studies solely evaluated INCS spray compared to placebo (30–41). One study had two separate treatment arms comparing 1) INCS spray only *vs* placebo and 2) INCS spray with orally inhaled corticosteroids *vs* orally inhaled corticosteroids (42). The results of the two treatment arms were included in the relevant subgroup analyses. Three studies compared INCS spray with concurrent orally inhaled corticosteroids *vs* orally inhaled corticosteroids (43–45). Two studies compared nasal inhalation of corticosteroids via spacer and nozzle *vs* nasal inhalation of placebo (46, 47).

Risk of bias in the included studies

The included studies appeared to have an overall low risk of bias (Fig. 2). All studies stated that the method of treatment allocation was random, with four studies specifically describing the method of randomization (31, 33, 35, 39). Fourteen studies had an unclear allocation concealment corresponding to a Cochrane B grade. Baseline data for all outcomes were provided in all studies, and none of the studies had significant pretreatment differences between groups. Withdrawals and dropouts were accounted for in 17 trials and could be deduced for the one remaining study (30). Intention-to-treat and per-protocol analyses were performed in two studies (31, 43).

Forced expiratory volume in 1 s

Ten of the 18 trials measured changes in Forced Expiratory Volume in 1 s (FEV1) after some form of INCS medication. Pooling data from the five trials reporting FEV1 outcomes as percent predicted demonstrated a significant improvement of 2.10% (95% CI, 0.21–3.99%) favoring treatment with any form of INCS (34, 35, 38, 40, 44). FEV1 was expressed in raw data as liters in the remaining five studies and pooling of these data found a nonsignificant improvement of 0.09 (95% CI, –0.04 to 0.22) in patients undergoing treatment with INCS (30, 32, 39, 42, 43). A pooled analysis of nine studies using the SMD found a nonsignificant improvement in FEV1 with active treatment (SMD = 0.16; 95% CI, –0.03 to 0.36; $P = 23\%$) (Fig. 3).

Subgroup analysis was performed on eight studies comparing INCS spray to placebo without concurrent treatment with orally inhaled corticosteroids. The SMD favored INCS spray compared to placebo, yielding an improvement of 0.31 (95% CI, 0.04–0.58; $P = 20\%$) (30, 32, 34, 35, 38–40, 42). This difference was seen in studies reporting FEV1 as percent predicted and in those reporting absolute values in liters (WMD = 2.30%; 95% CI, 0.37–4.24 and WMD = 0.19; 95% CI, 0.06 to 0.32, respectively). Three trials evaluated INCS spray in addition to baseline administration of orally inhaled corticosteroids (42–44). Analysis of the SMD found no difference between groups (0.04, 95% CI, –0.15 to 0.22; $P = 0\%$). The subgroup of studies evalu-

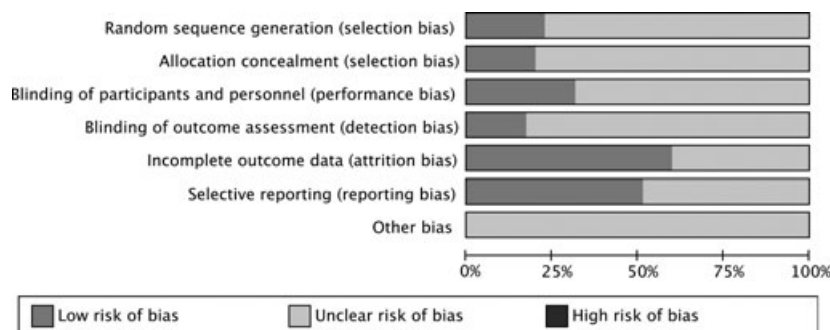


Figure 2 Risk of bias graph. Risk of bias assessed using the Cochrane 'Risk of bias' tool and reported as percentages across all included studies.

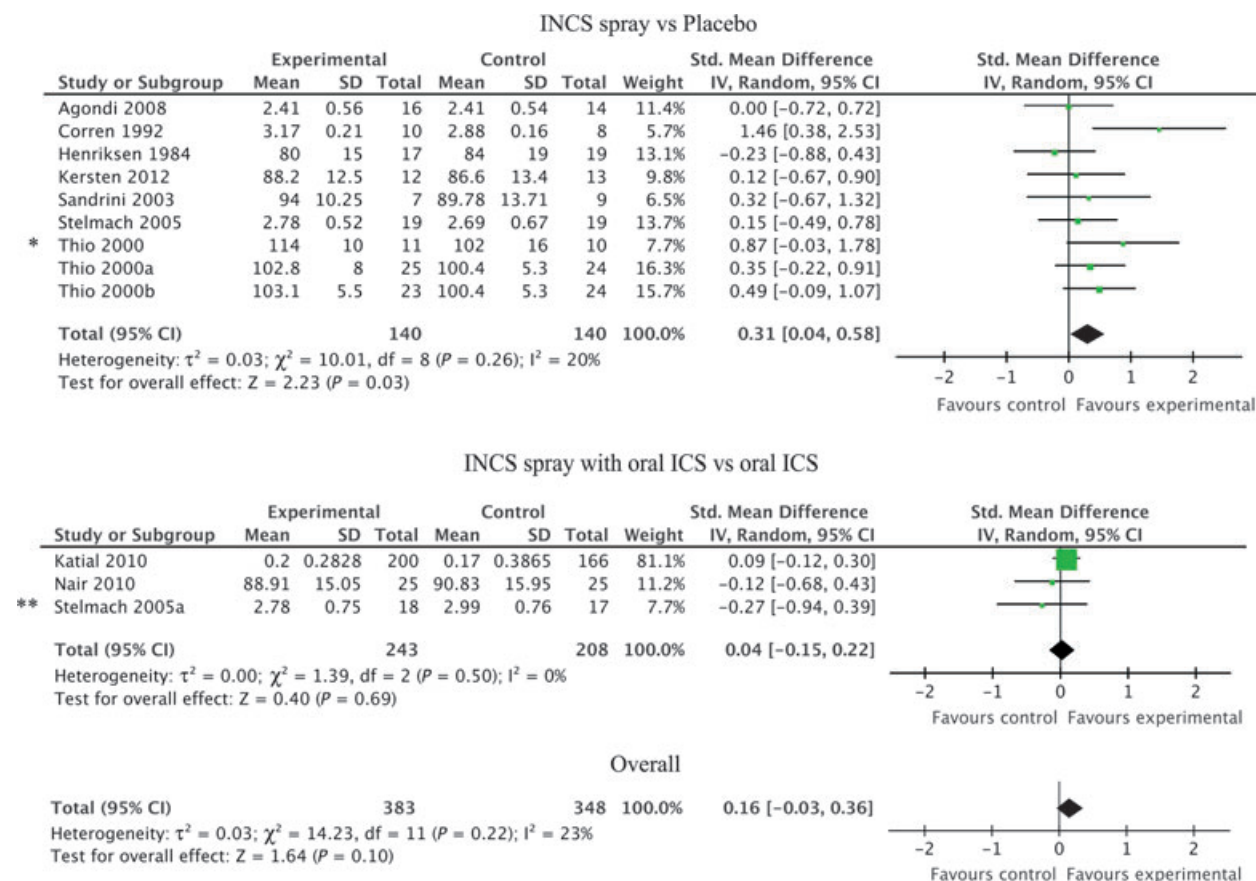


Figure 3 Changes in FEV1. Forest plot of changes in FEV1 using the standardized mean difference. INCS, intranasal corticosteroid; SD, standard deviation; CI, confidence interval; ICS, inhaled corticosteroid; IV, inverse variance. *Data from two separate studies reported as one publication. Data extracted from three parallel experimental arms: Thio 2000 (200 µg FP aqueous nasal spray vs placebo); Thio

2000a (200 µg FP aqueous nasal spray vs placebo); Thio 2000b (400 µg BDP aqueous nasal spray vs placebo). **Data extracted from two parallel experimental arms: Stelmach 2005 (400 µg BDP aqueous nasal spray with placebo MDI vs placebo nasal spray with placebo MDI); Stelmach 2005a (400 µg BDP aqueous nasal spray with 1000 µg BDP MDI vs placebo nasal spray with 1000 µg BDP MDI).

ating nasal inhalation of corticosteroids did not assess FEV1 as an outcome.

Peak expiratory flow

A total of eight studies assessed morning oral peak expiratory flow (PEF) in patients treated with any INCS medication as compared to placebo (32–34, 43–47). Morning PEF measures demonstrated a nonsignificant increase of 13.15 l/min (95% CI, -1.13 to 27.43; $P = 67\%$) with INCS (all forms) treatment. Subgroup analysis of studies comparing INCS spray to placebo without concurrent treatment with orally inhaled corticosteroids found no change in PEF (SMD = -11.78; 95% CI, -54.04 to 30.47; $P = 0\%$) (32–34). Similarly, meta-analysis of studies evaluating INCS spray in addition to baseline administration of orally inhaled corticosteroids found no difference in PEF (SMD = 0.43; 95% CI, -10.10 to 10.96; $P = 39\%$) (33, 43–45). Pooling of the two studies comparing nasally inhaled corticosteroids to placebo found a significant increase in PEF (WMD = 34.07; 95% CI, 20.87 to 47.27, $P = 0\%$) favoring the active treatment group (46, 47).

Six of the eight studies assessing morning PEF also evaluated evening PEF in patients treated with any INCS medication. Meta-analysis of these data found a nonsignificant change in evening PEF of 2.37 l/min (95% CI, -4.93 to 9.68; $P = 11\%$). Analyses of studies comparing INCS spray to placebo without concurrent treatment with orally inhaled corticosteroids found no difference (SMD = -26.65; 95% CI, -74.33 to 21.02; $P = 0\%$). Similarly, meta-analysis of studies evaluating INCS spray in addition to baseline administration of orally inhaled corticosteroids found no difference in final PEF between active treatment groups and placebo groups (SMD = -2.37; 95% CI, -9.92 to 5.18, $P = 0\%$). The two studies comparing nasally inhaled corticosteroids to nasally inhaled placebo demonstrated a significant improvement in PEF of 14.20 l/min (95% CI, 2.06 to 26.34, $P = 0\%$) favoring the active treatment group (46, 47).

Bronchial challenge

Seven studies described airway hyper-responsiveness using either histamine or methacholine challenge (30, 32, 38,

40–42, 44). Six of the seven studies expressed the results as the dose provoking a 20% decrease in forced expiratory volume in 1 s (PC20 or PD20) (30, 32, 38, 41, 42, 44). Thio et al. was the only study to express the results of three parallel groups as the logPD20 and was therefore analyzed separately. Meta-analysis found an improvement in PC20 of 0.43 (95% CI, 0.16–0.69) in favor of treatment with any form of INCS. Subgroup analyses found an improvement in PC20 of 0.46 (95% CI, 0.12–0.79) in studies comparing only INCS spray to placebo and no improvement in studies evaluating INCS spray in addition to baseline administration of orally inhaled corticosteroids (WMD = 0.38; 95% CI, –0.05 to 0.81). An analysis of results from Thio et al. did not find a significant difference between INCS spray and placebo (WMD = –0.22; 95% CI, –0.58 to 0.15). There was no significant heterogeneity between studies for any results. The subgroup of studies administering nasally inhaled

corticosteroids did not report bronchial reactivity as an outcome.

Asthma symptoms scores

Nine trials reported asthma symptom scores using various scales (Fig. 4) (30, 32, 34, 35, 38, 41–43, 45, 47). The pooled data analysis of these nine studies demonstrated a significant improvement in asthma symptom scores of 0.69 (95% CI, 0.04–1.35) between patients receiving INCS (any form) vs placebo (30, 32, 34, 35, 38, 41–43, 45, 47). Subgroup analyses of studies comparing only INCS spray to intranasal placebo also found an improvement in symptom scores of 0.42 (95% CI, 0.03–0.53) (30, 32, 34, 38, 41, 42). Three trials compared INCS spray with concurrent administration of orally inhaled corticosteroids to orally inhaled corticosteroids alone. The pooled analysis of these three studies showed no significant

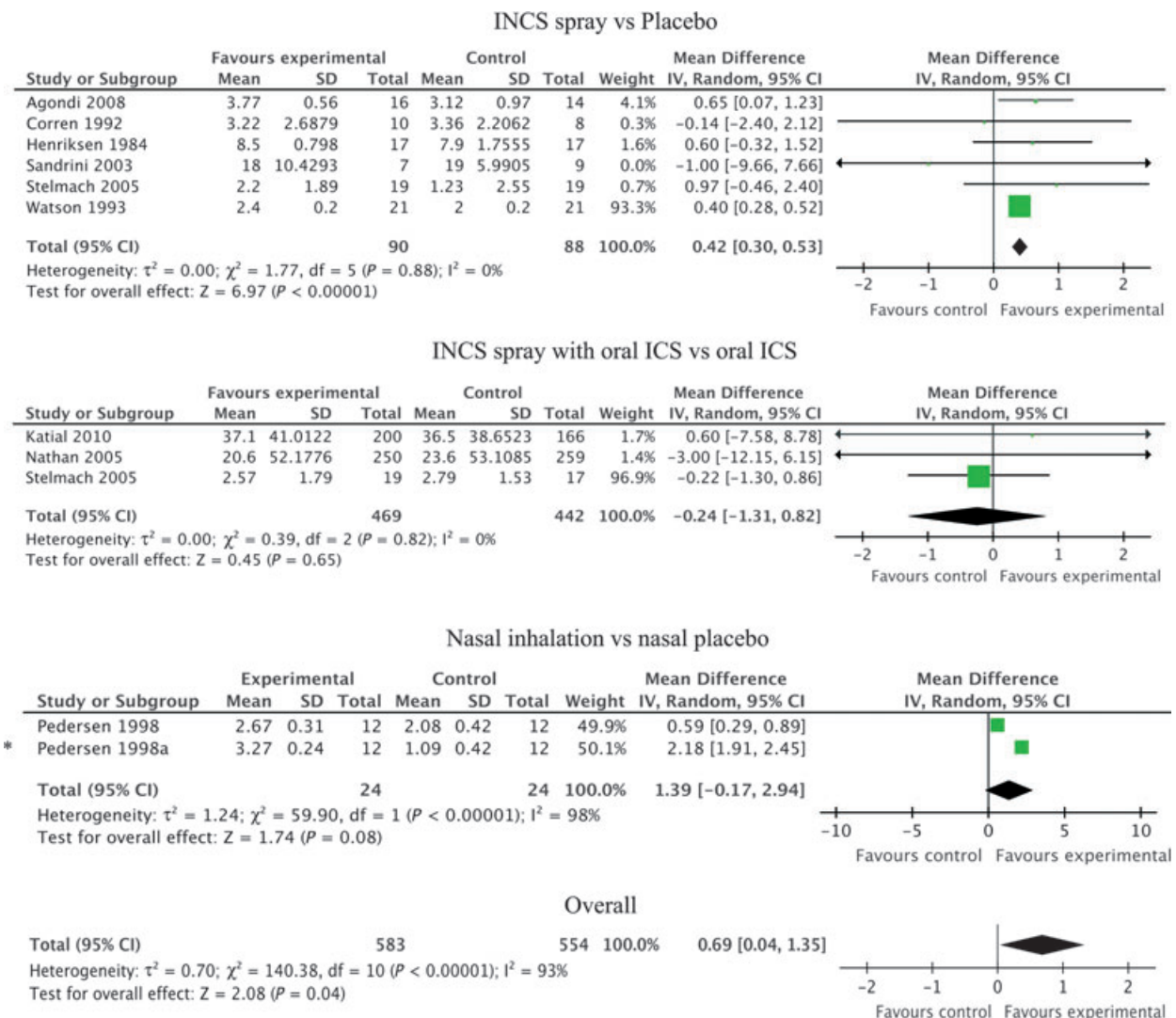


Figure 4 Changes in Asthma Symptom Scores. Forest plot of changes in asthma symptom scores using the standardized mean difference. INCS, intranasal corticosteroid; SD, standard deviation;

CI, confidence interval; ICS, inhaled corticosteroid; IV, inverse variance. *Double-blind, placebo-controlled, cross-over trial. Data extracted as though from two different studies.

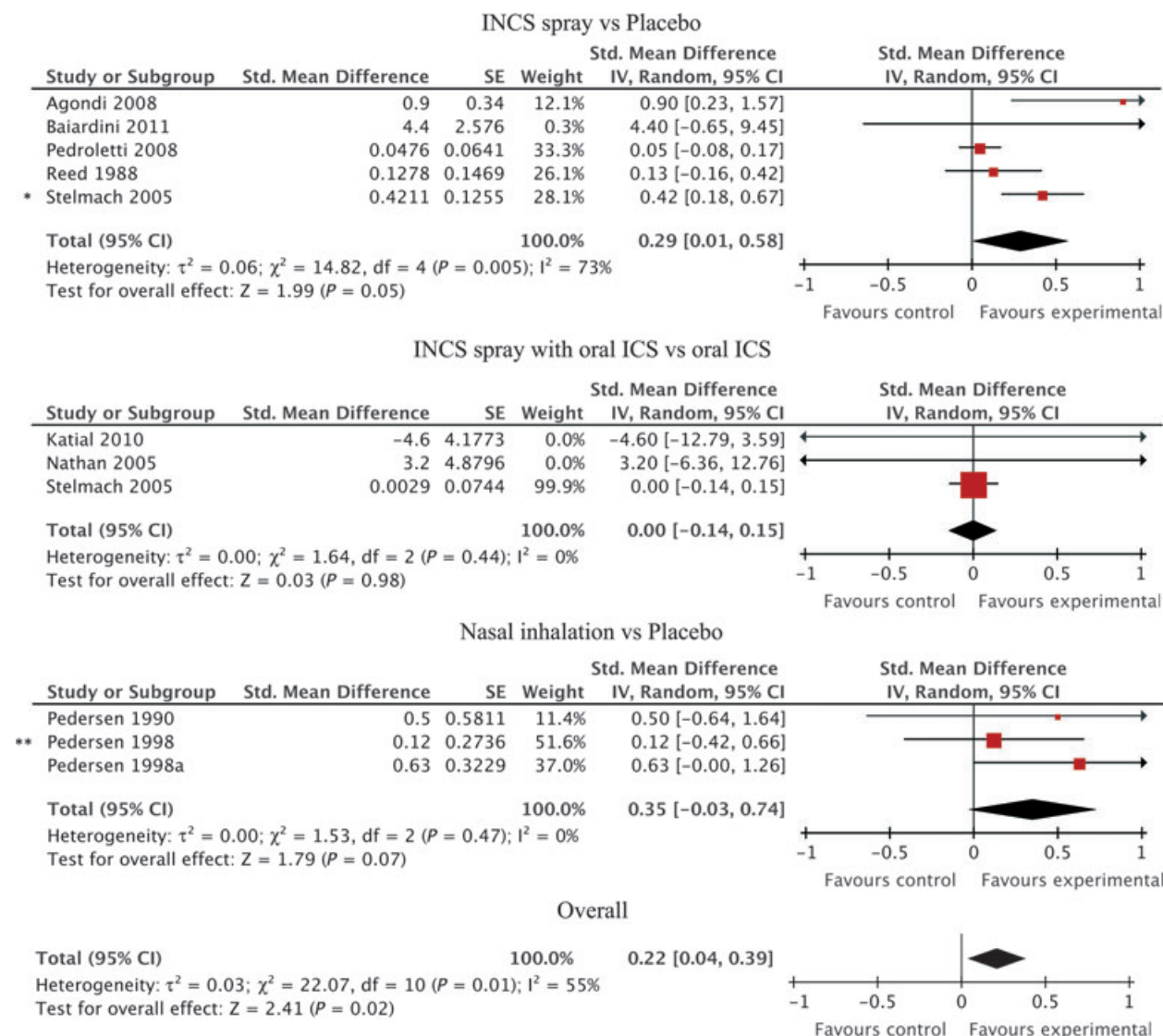


Figure 5 Changes in rescue medication use. Forest plot of changes in rescue medication use using the standardized mean difference. INCS, intranasal corticosteroid; SD, standard deviation; CI, confidence interval; ICS, inhaled corticosteroid; IV, inverse variance. *Data extracted from two parallel experimental arms: Stelmach

2005 (400 µg BDP aqueous nasal spray with placebo MDI vs placebo nasal spray with placebo MDI); Stelmach 2005a (400 µg BDP aqueous nasal spray with 1000 µg BDP MDI vs placebo nasal spray with 1000 µg BDP MDI). **Double-blind, placebo-controlled, cross-over trial. Data extracted as though from two different studies.

difference (SMD = -0.24; 95% CI, -1.31 to 0.82) in asthma symptom scores. Lastly, the two studies comparing nasally inhaled corticosteroids to placebo each individually showed improvement in asthma symptom scores; however, pooled analysis demonstrated a nonsignificant improvement in asthma symptom scores with active treatment (WMD = 1.39; 95% CI, -0.17 to 2.94) (46, 47).

Quality of life

Four studies assessed asthma-specific Quality of life (QOL) (31, 35, 39, 44). One study evaluated QOL using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) for the comparison of INCS spray to intranasal placebo (mean differ-

ence = 0.20; 95% CI, -0.19 to 0.59) (35). A second study used the Juniper Mini Asthma Quality of Life Questionnaire for the comparison of INCS spray plus orally inhaled corticosteroids to orally inhaled corticosteroids alone, showing no difference (mean difference = -0.11; 95% CI, -0.56 to 0.34) (44). The results of these two studies were combined for meta-analysis and revealed a nonsignificant overall improvement of 0.04 in QoL units (95% CI, -0.42 to 0.49) (35, 44). Of the two remaining studies assessing changes in QoL, neither reported values in a manner that allowed pooling of the data for meta-analysis. However, both Baiardini et al. and Scichilone et al. reported significant improvement in lower airway QOL with the use of INCS spray compared to placebo ($P < 0.001$ and $P = 0.006$, respectively). Neither of

the studies evaluating nasally inhaled corticosteroids assessed patients' quality of life.

Rescue medication use

Nine of the 18 included studies described rescue medication use during the trial period, and two of the nine studies reported results for two parallel groups (42, 47). The results were reported using different scales, which included both continuous and dichotomous measures. Meta-analysis of all forms of INCS was performed using generic variance method, demonstrating a significant change of 0.22 (95% CI, 0.04–0.39) (30, 31, 36, 37, 42, 43, 45–47). Subgroup analysis of studies comparing INCS spray to placebo without concurrent treatment with orally inhaled corticosteroids found a similar decrease during the trial period (SMD = 0.29; 95% CI, 0.01–0.58) (Fig. 5). The pooled data of studies evaluating INCS spray in addition to baseline administration of orally inhaled corticosteroids found no difference (SMD = 0.00; 95% CI: –0.14 to 0.15). The pooled analysis of the two studies comparing nasally inhaled corticosteroids to placebo found a nonsignificant difference in rescue medication use (WMD = 0.35; 95% CI, –0.03 to 0.74) (46, 47).

Discussion

This systematic review with meta-analysis of 18 RCTs in patients with comorbid asthma and AR demonstrated improvement in some but not all asthma-specific outcome metrics with the use of intranasal corticosteroid medications (Table 2). Significant improvements were seen in FEV1, morning PEF, bronchial challenge, asthma-specific symp-

toms, and rescue medication use, but results were variable based on method of administration (spray vs inhalation) and use of concurrent orally inhaled corticosteroids. The most consistent results were seen when INCS sprays were used without concurrent orally inhaled corticosteroids or when corticosteroids were inhaled through the nose and into the lungs.

The variable results seen across studies are not unexpected, considering differences in route of administration, baseline control of asthma, and inclusion of both adults and children. Findings from subgroup analyses indicate that INCS sprays are most efficacious in improving asthma-specific outcomes in patients not already on orally inhaled corticosteroids while not providing any significant improvements in patients already on daily-inhaled corticosteroids. This finding may reflect the fact that patients on orally inhaled corticosteroids already have baseline control of lower airway inflammation and thus less room for improvement with additional medication. Overall, asthma severity for most subjects in the included trials was mild. The presence of asthma was necessary for entry into each trial; however, patients were not required to have ongoing symptoms, depressed pulmonary function, or need for rescue medications. The majority of trials actually excluded patients with severe asthma or asthma exacerbations within 1–3 months of the study start (Table 2).

The results of this study do lend support to the unified airway theory, namely that treatment of the upper airway can affect lower airway function. This was especially true in regard to outcomes measuring pulmonary function and bronchial hyper-reactivity, suggesting that a decrease in upper airway inflammation may lead to a decrease in lower airway reactivity.

Table 2 Results of meta-analysis

Outcomes	Overall change (95% CI)	INCS spray vs Placebo	INCS + oral ICS vs oral ICS	Nasally inhaled corticosteroids vs Placebo
Forced expiratory volume in 1 s				
FEV1% (WMD)	2.10 (0.21, 3.99)	2.30 (0.37, 4.24)	–1.92 (–10.52, 6.68)	
FEV1 (L) (WMD)	0.09 (–0.04, 0.22)	0.19 (0.06, 0.32)	0.03 (–0.04, 0.10)	
FEV1 (L) (SMD)	0.16 (–0.03, 0.36)	0.31 (0.04, 0.58)	0.04 (–0.15, 0.22)	
Peak expiratory flow				
Morning PEF (l/min) (WMD)	13.15 (–1.13, 27.43)	–11.78 (–54.04, 30.47)	0.43 (–10.10, 10.96)	34.07 (20.87, 47.27)
Evening PEF (l/min) (WMD)	2.37 (–4.93, 9.68)	–26.65 (–74.33, 21.02)	–2.37 (–9.92, 5.18)	14.20 (2.06, 26.34)
Bronchial reactivity				
PC20 (WMD)	0.43 (0.16, 0.69)	0.46 (0.12, 0.79)	0.38 (–0.05, 0.81)	
Asthma symptom scores				
Asthma symptoms (WMD)	0.69 (0.04, 1.35)	0.42 (0.30, 0.53)	–0.24 (–1.31, 0.82)	1.39 (–0.17, 2.94)
Rescue medication use				
Rescue medication use (SMD)	0.22 (0.04, 0.39)	0.29 (0.01, 0.58)	0.00 (–0.14, 0.15)	0.35 (–0.03, 0.74)

CI, confidence interval; INCS, intranasal corticosteroid; ICS, inhaled corticosteroid; WMD, weighted mean difference; SMD, standardized mean difference; PC20, dose of methacholine or histamine provoking a > 20% decrease in FEV1.

The findings also suggest that INCS sprays directly treating the upper airway can improve lower airway-specific symptoms and need for rescue medication usage. It could be argued that treatment effects observed across studies may result from deposition of intranasal corticosteroids into the lungs. However, multiple studies assessing drug delivery of intranasal sprays have failed to show significant deposition of medication into the lower airways (49–51). Therefore, we can assume that the improvements seen in the lower airways are likely the result of targeted treatment of inflammation in the upper airways. In contrast, the available evidence suggests that the use of nasally inhaled nebulized medication may result in significant deposition of drugs in the lungs (up to 58%) (49–51). Thus, improvements noted with nasally inhaled steroids could be due to pulmonary deposition and/or improvements in upper airway inflammation.

INCS sprays are considered a first-line treatment to control upper airway inflammation in patients with AR. Although this meta-analysis suggests that treatment of the upper airway can improve some lower airway outcome measures, the direct clinical implications are less straightforward. For example, INCS sprays resulted in statistically significant improvements in some pulmonary function measurements, but the degree of change may not necessarily be clinically relevant to the individual patient. It therefore remains unclear whether INCS sprays may be a sufficient monotherapy for asthma control in patients with AR and mild asthma. The data suggest that the addition of INCS sprays to orally inhaled corticosteroids adds little additional benefit for asthma-specific outcomes in patients with mild asthma, although it remains unknown whether an effect would exist in patients with moderate or severe asthma. Lastly, the technique of nasal inhalation of corticosteroids seems to hold promise as a single therapy, which would address both upper and lower airway inflammation. Although only two studies examined this modality specifically, asthma-specific outcomes were consistently improved compared to placebo. One additional study not included in the meta-analysis compared nasal inhalation of corticosteroids to orally inhaled corticosteroids (52). This study found no significant differences between the two groups for any asthma outcomes (FEV1, asthma symptoms, rescue medica-

tion use), suggesting that the efficacy of nasally inhaled corticosteroids may be similar to orally inhaled corticosteroids, although the study was not designed as a formal noninferiority study. Further research efforts therefore might focus on nasally inhaled corticosteroid medications as a single therapy that could potentially improve efficiency, compliance, and costs.

Conclusion

Intranasal corticosteroid medications significantly improve some asthma-specific outcome measures in patients suffering from both AR and asthma. This effect was most pronounced with INCS sprays when patients were not on daily orally inhaled corticosteroids, or when corticosteroid medications were inhaled through the nose into the lungs. Further research is needed to clarify the role of INCS sprays as asthma-specific therapy, as well as the role of the nasal inhalation technique as a monotherapy in patients suffering from both asthma and AR.

Author contributions

Shivangi Lohia: Developed protocol, performed literature search, extracted data, performed data analysis, drafted the final review.

Rodney J. Schlosser: Responsible for conception and design of review, performed literature search, revised the final review.

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