

# Effects of double-dose intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis

Likhit Khattiyawittayakun, MD<sup>1,2</sup>, Kachorn Seresirikachorn, MD<sup>1,3</sup> , Wirach Chitsuthipakorn, MD<sup>4</sup> ,  
Dichapong Kanjanawasee, MD<sup>1,3</sup>  and Kornkiat Snidvongs, MD, PhD<sup>1,3</sup> 

**Background:** When a standard dose of intranasal corticosteroid (INCS) fails to control symptoms of allergic rhinitis (AR), a double dose of INCS is optional. This systematic review aimed to assess the effects of double-dose INCS.

**Methods:** Literature searches were performed using MEDLINE and EMBASE. Randomized controlled trials that studied the effects of double-dose INCS vs standard-dose INCS for treating patients with AR were included. Data from the included studies were extracted and collected for meta-analyses. The outcomes were nasal symptoms, ocular symptoms, and adverse events.

**Results:** Twelve studies (4166 patients) met the inclusion criteria. There were 5 pediatric studies (1868 patients), 5 adult studies (1414 patients), and 2 studies with mixed populations (884 patients). The meta-analysis results in adult patients favored the effects of double-dose INCS on: total nasal symptom score (standardized mean difference [SMD]  $-0.25$ ; 95% confidence interval [CI],  $-0.41$  to  $-0.08$ ; 4 studies; 568 patients) and total ocular symptom score (SMD  $-0.27$ ; 95% CI,  $-0.52$  to  $-0.03$ ; 1 study; 259 patients). The meta-analysis results in pediatric patients did not show

the difference between groups on total nasal symptom score (SMD  $-0.16$ ; 95% CI,  $-0.40$  to  $0.07$ ; 3 studies; 801 patients). The meta-analysis of ocular symptom score in pediatric patients had insufficient data. There were no differences between groups on adverse events.

**Conclusion:** Double-dose INCS showed better improvement in nasal and ocular symptoms in adult patients with AR when compared to the standard dose. These beneficial effects were not seen in the pediatric population. Adverse events between groups were not different. © 2018 ARS-AAOA, LLC.

**Key Words:** steroids; corticosteroids; intranasal; rhinitis; allergic rhinitis

## How to Cite this Article:

Khattiyawittayakun L, Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Effects of double-dose intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2018;00:1-7.

Intranasal corticosteroids (INCSs) are recommended by international guidelines as first-line drugs for patients

with allergic rhinitis (AR). INCSs may be prescribed to AR patients with persistent symptoms, moderate to severe in severity, or have nasal obstruction as a major symptom.<sup>1,2</sup> INCSs bind to a specific cytoplasmic glucocorticoid receptor then activate anti-inflammatory gene transcription and repress pro-inflammatory gene transcription.<sup>3</sup> As a result, lymphocyte activation and cytokine production are inhibited, which decrease inflammatory cells migration to the nasal mucosa.<sup>4,5</sup> The anti-inflammatory effects of INCSs effectively control the allergic response and relieve the clinical symptoms including itching, sneezing, rhinorrhea, nasal obstruction, and ocular symptoms.

High glucocorticoid receptor occupancy allows INCSs to bind to most glucocorticoid receptors in the nasal mucosa, which enhances the effects of INCSs. There are several studies assessing glucocorticoid receptor occupancy.<sup>6</sup> Boger et al.<sup>7</sup> revealed a relationship between the receptor occupancy and the dosage of corticosteroid in rats with 3 doses

<sup>1</sup>Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; <sup>2</sup>Department of Otolaryngology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand; <sup>3</sup>Endoscopic Nasal and Sinus Surgery Excellent Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; <sup>4</sup>Department of Otolaryngology, Sawan Pracharak Hospital, Nakhon Sawan, Thailand

Correspondence to: Kornkiat Snidvongs, MD, PhD, Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, 1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand; e-mail: drkornkiat@yahoo.com

Potential conflict of interest: K.Sn. received Honoraria for speaking at symposia from Merck Sharp & Dohme, Meda, and Menarini. K.Se., W.C., D.K., and L.K. declare that they have no conflicts of interest. Presented orally at the Annual ARS Meeting on September 20, 2014 in Orlando, FL.

Received: 1 June 2018; Revised: 9 August 2018; Accepted: 14 August 2018  
DOI: 10.1002/alr.22204  
View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).

of intravenous fluticasone propionate. Although the association between dosage of INCS and glucocorticoid receptor occupancy in humans has never been reported, there are several randomized controlled trials assessing the clinical responses to various doses of INCSs in patients with AR. When a standard dose of INCS fails to control AR symptoms, doubling the dosage of INCS is an option for further medical treatment prior to considering immunotherapy.<sup>1</sup> This systematic review aimed to assess the effects of a double dose of INCS for treating AR.

## Materials and methods

### Eligibility criteria

#### *Inclusion criteria*

Types of studies: randomized controlled trials (RCTs).

Types of participants: AR patients of all ages. The diagnostic criteria of AR followed the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.<sup>1</sup>

Types of interventions: double-dose vs standard-dose INCS, any treatment duration.

#### *Exclusion criteria*

Trials published in a language other than English.

Trials that studied mixed populations of AR and non-AR were excluded unless it was possible to isolate the outcomes for patients with AR.

Types of outcome measures: nasal and ocular symptoms, disease-specific quality of life, objective tests for nasal patency, and adverse events.

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for preferred reporting items.<sup>8</sup>

### Information sources and search strategy

Electronic systematic searches and manual searches for RCTs were conducted with no publication year, or publication status restrictions. The date of the last search was October 6, 2017. The literature searches were performed using MEDLINE and EMBASE. References of included studies and additional sources were searched.

### Study selection process

Two review authors (L.K., K.Se.) independently performed the trial selections, including screening the title and abstract of the articles based on the predetermined eligibility criteria and reviewing the full text of the screened articles.

### Data extraction

Three review authors (L.K., K.Se., D.K.) extracted the details of the included studies. The corresponding authors were approached for further information when there was insufficient information or conflicting data. Any disagreements over the data were resolved by the fifth author (K.Sn.) if necessary.

Data from the pediatric and adult populations were extracted and analyzed separately. The extracted data were study type, number of participants, mean age, gender, number of subjects lost to follow-up, the forms and dosages of INCSs, and duration of treatment. When multiple dosages of INCSs were used in a study, the highest dose within the range of standard dose was selected for data extraction. The selected standard dose was one-half of the selected double dose. The primary outcome was the change score from baseline of total nasal symptom. The secondary outcomes were the change scores from baseline of individual nasal symptoms, ocular symptoms, disease-specific quality of life, objective tests for nasal patency, and adverse events. When the change scores were not reported, the final values were collected.<sup>9</sup>

### Risk of bias in individual studies

The quality of included studies was assessed by evaluating the risks of bias as guided by the Cochrane Handbook for Systematic Reviews of Interventions.<sup>9</sup> Five domains were assessed including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. The included studies had low risk of bias when the methods used for each domain were clearly described. They had high risk of bias when the methods used for each domain had high risk. When there was not enough information to determine the risk, the RCT was defined as unclear risk of bias.

### Data synthesis and summary measures

Data were pooled for meta-analysis. Risk ratio (RR) and 95% confidence intervals (CIs) were used for dichotomous data such as adverse events. Standardized mean difference (SMD) and 95% CIs were used for continuous data such as symptom scores. The significance of discrepancies in the estimates of treatment effects was assessed by measurement of the  $I^2$  statistic. An  $I^2$  of less than 40%, 40% to 60%, and greater than 60% represented low, moderate, and substantial heterogeneity, respectively. A fixed-effect method was used when statistical heterogeneity was low. When statistical heterogeneity was high, a random-effect method was used for a more conservative estimate of the difference. Statistical assessments were performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).<sup>10</sup>

## Results

### Study selection

There were 2442 studies identified and retrieved (2440 studies were from electronic searches and 2 studies from manual searches). During the title and abstract screening, 2391 studies were excluded. Fifty-one studies were assessed for eligibility. Thirty-nine studies were removed after full-text screening. Reasons for exclusion are listed in Figure 1. Twelve RCTs (4166 patients) were included in the

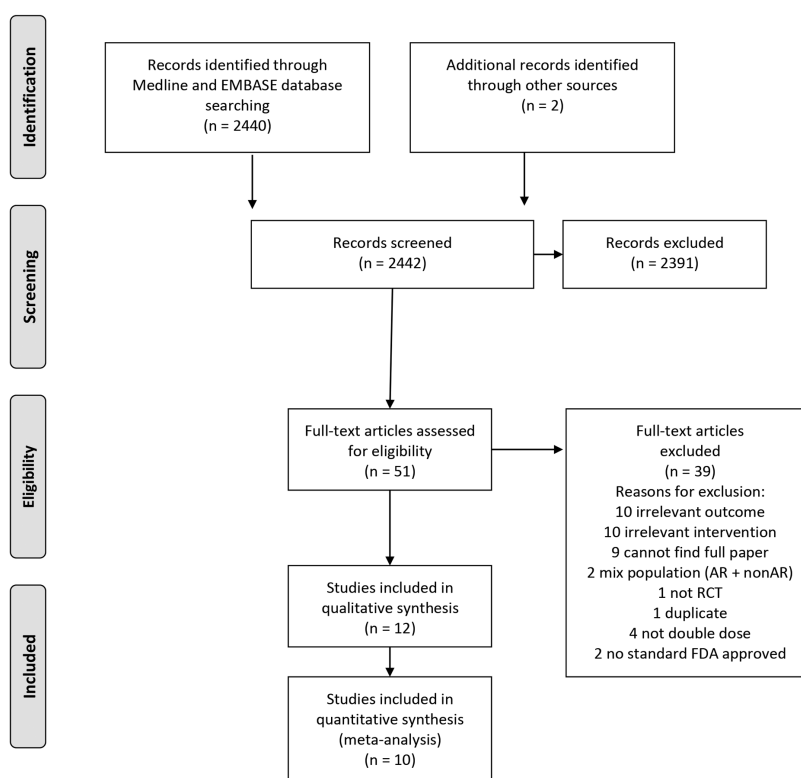


FIGURE 1. Flow diagram of study selection. AR = allergic rhinitis; RCT = randomized controlled trial.

qualitative synthesis.<sup>11–22</sup> Five RCTs studied the pediatric population, 5 RCTs studied the adult population, and 2 RCTs studied mixed populations. The 2 RCTs of mixed population were excluded from meta-analysis because the separate data between children and adult patients could not be extracted or calculated.<sup>15,17</sup> A total of 10 RCTs (3282 patients) were included for meta-analysis. Characteristics of the included studies are shown in Table 1. A flowchart of study retrieval and selection is presented in Figure 1.

### Pediatric study

There were 5 RCTs that studied the pediatric population with 1868 participants. The mean age of the patients was 9.05 years old and 60% of the patients were male.<sup>11,13,16,18,21</sup> All patients were diagnosed with seasonal AR confirmed by either skin test or serum specific immunoglobulin E (IgE). There were 1061 patients that received either a standard dose or a double dose of INCS. The INCSs used in these RCTs were budesonide,<sup>11</sup> beclomethasone dipropionate,<sup>21</sup> fluticasone propionate,<sup>13,16</sup> and mometasone furoate.<sup>18</sup> Duration of treatment ranged from 14 to 28 days.

The meta-analysis results showed no statistically significant difference in total nasal symptom score between groups (SMD  $-0.16$ ; 95% CI,  $-0.40$  to  $0.07$ ; 3 studies; 801 patients<sup>11,18,21</sup>). An  $I^2$  of 53% represented moderate heterogeneity (Fig. 2). When individual symptoms were analyzed, there were no statistically significant differences

between groups in: nasal obstruction (SMD  $-0.01$ ; 95% CI,  $-0.18$  to  $0.16$ ; 2 studies; 533 patients;  $I^2$  0%<sup>11,21</sup>); rhinorrhea (SMD  $-0.03$ ; 95% CI,  $-0.20$  to  $0.14$ ; 2 studies; 533 patients;  $I^2$  0%<sup>11,21</sup>); sneezing (SMD  $-0.15$ ; 95% CI,  $-0.53$  to  $0.22$ ; 2 studies; 533 patients;  $I^2$  51%<sup>11,21</sup>); and itching (SMD  $0.00$ ; 95% CI,  $-0.21$  to  $0.21$ ; 1 study; 479 patients<sup>21</sup>). Although 2 RCTs assessed the total ocular symptom score, meta-analysis of the total ocular symptom score could not be performed because the standard deviation was neither reported nor imputed.<sup>13,16</sup> None of the included RCTs assessed disease-specific quality of life or peak nasal inspiratory flow rate.

### Adult study

Five RCTs studied 1414 adult participants.<sup>12,14,19,20,22</sup> The mean age of the patients (reported in 5 trials<sup>12,14,19,20,22</sup>) was 35.9 years old and 42% of the patients were male (reported in 4 trials<sup>12,14,19,20,22</sup>). There were 689 patients that received either a standard dose or a double dose of INCS. All patients were diagnosed with AR confirmed by either skin test or serum specific IgE. Four of the included studies assessed patients with seasonal AR<sup>14,19,20,22</sup> while 1 study assessed perennial AR.<sup>12</sup> The INCSs used were budesonide,<sup>12,14,19</sup> triamcinolone acetonide,<sup>20</sup> and fluticasone furoate.<sup>22</sup> Duration of treatment ranged from 14 to 42 days.

The meta-analysis results favored the effects of the double-dose over the standard-dose INCS on total nasal

TABLE 1. Characteristics of included studies

| Reference                       | Year | Patient                 | Criteria by age (years old) | Patients (n) | INCS                        | Standard dose ( $\mu\text{g/day}$ ) | Double dose ( $\mu\text{g/day}$ ) | Duration of treatment (days) |
|---------------------------------|------|-------------------------|-----------------------------|--------------|-----------------------------|-------------------------------------|-----------------------------------|------------------------------|
| <b>Pediatric studies</b>        |      |                         |                             |              |                             |                                     |                                   |                              |
| Agertoft et al. <sup>11</sup>   | 1993 | SAR                     | 4–16                        | 83           | Budesonide                  | 200                                 | 400                               | 28                           |
| Grossman et al. <sup>16</sup>   | 1993 | SAR                     | 4–11                        | 250          | Fluticasone propionate      | 100                                 | 200                               | 14                           |
| Boner et al. <sup>13</sup>      | 1995 | SAR                     | 4–12                        | 143          | Fluticasone propionate      | 100                                 | 200                               | 28                           |
| Meltzer et al. <sup>18</sup>    | 1999 | SAR                     | 6–11                        | 679          | Mometasone furoate          | 100                                 | 200                               | 28                           |
| Storms et al. <sup>21</sup>     | 2013 | SAR, moderate to severe | 6–11                        | 713          | Beclomethasone dipropionate | 80                                  | 160                               | 14                           |
| <b>Adult studies</b>            |      |                         |                             |              |                             |                                     |                                   |                              |
| Irander et al. <sup>14</sup>    | 1984 | SAR                     | 15–66                       | 118          | Budesonide                  | 200                                 | 400                               | 28                           |
| Pederson et al. <sup>19</sup>   | 1994 | SAR                     | 17–61                       | 180          | Budesonide                  | 200                                 | 400                               | 28                           |
| Andersson et al. <sup>12</sup>  | 1995 | PAR                     | NR                          | 98           | Budesonide                  | 200                                 | 400                               | 42                           |
| Rosenthal et al. <sup>20</sup>  | 1998 | SAR                     | 18–65                       | 377          | Triamcinolone acetonate     | 200                                 | 400                               | 14                           |
| Martin et al. <sup>22</sup>     | 2007 | SAR                     | $\geq 12$                   | 641          | Fluticasone furoate         | 220                                 | 440                               | 14                           |
| <b>Mixed population studies</b> |      |                         |                             |              |                             |                                     |                                   |                              |
| Meltzer <sup>17</sup>           | 1998 | PAR                     | $\geq 6$                    | 478          | Budesonide                  | 128                                 | 256                               | 42                           |
| Creticos et al. <sup>15</sup>   | 1998 | SAR                     | $\geq 6$                    | 406          | Budesonide                  | 128                                 | 256                               | 28                           |

INCS = intranasal corticosteroid; NR = not reported; PAR = perennial rhinitis; SAR = seasonal allergic rhinitis.

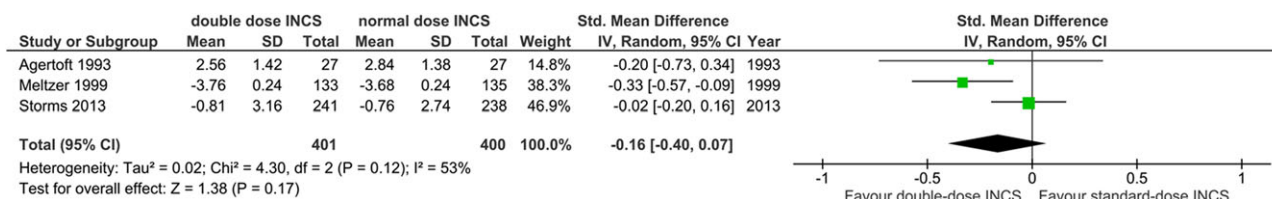


FIGURE 2. Improvement in total nasal symptom score in pediatric patients: double-dose vs standard-dose intranasal corticosteroid. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; INCS = intranasal corticosteroid; IV = inverse variance; Std. mean difference = standardized mean difference.

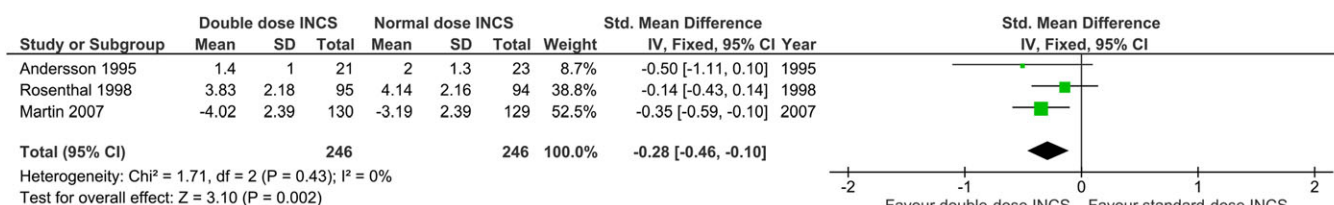


FIGURE 3. Improvement in total nasal symptom score in adult patients: double-dose vs standard-dose intranasal corticosteroid. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; INCS = intranasal corticosteroid; IV = inverse variance; Std. mean difference = standardized mean difference.

symptom score (SMD  $-0.28$ ; 95% CI,  $-0.46$  to  $-0.10$ ; 3 studies; 492 patients;  $I^2$  0%<sup>12,20,22</sup>; Fig. 3) and total ocular symptom score (SMD  $-0.27$ ; 95% CI,  $-0.52$  to  $-0.03$ ; 1 study; 259 patients<sup>22</sup>). When individual symptoms were analyzed, the effects favored the double-dose over the standard-dose INCS on: nasal obstruction (SMD  $-0.20$ ; 95% CI,  $-0.38$  to  $-0.03$ ; 3 studies; 492 pa-

tients,  $I^2$  0%<sup>12,20,22</sup>; Fig. 4); rhinorrhea (SMD  $-0.22$ ; 95% CI,  $-0.40$  to  $-0.04$ ; 3 studies; 492 patients;  $I^2$  0%<sup>12,20,22</sup>; Fig. 5); and itching (SMD  $-0.20$ ; 95% CI,  $-0.39$  to  $-0.02$ ; 2 studies; 448 patients;  $I^2$  17%<sup>20,22</sup>; Fig. 6). There were no statistically significant differences between groups in sneezing (SMD 0.00; 95% CI,  $-0.34$  to  $0.34$ ; 3 studies; 492 patients;  $I^2$  66%<sup>12,20,22</sup>) and peak nasal inspiratory flow rate

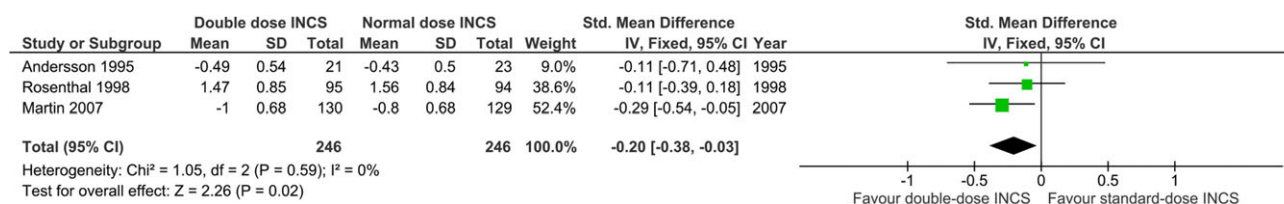


**FIGURE 4.** Improvement in nasal obstruction score in adult patients: double-dose vs standard-dose intranasal corticosteroid. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; INCS = intranasal corticosteroid; IV = inverse variance; Std. mean difference = standardized mean difference.

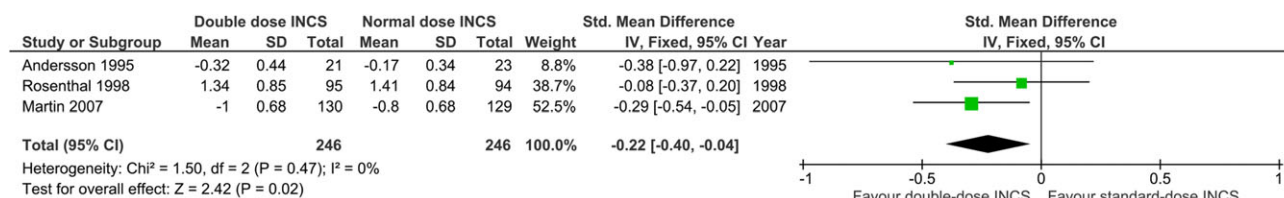


**FIGURE 5.** Improvement in rhinorrhea score in adult patients: double-dose vs standard-dose intranasal corticosteroid. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; INCS = intranasal corticosteroid; IV = inverse variance; Std. mean difference = standardized mean difference.

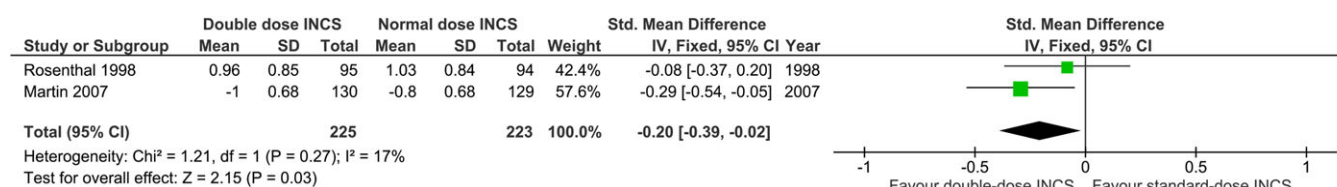


**FIGURE 6.** Improvement in itching score in adult patients: double-dose vs standard-dose intranasal corticosteroid. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; INCS = intranasal corticosteroid; IV = inverse variance; Std. mean difference = standardized mean difference.

(SMD  $-0.25$ ; 95% CI,  $-0.60$  to  $0.10$ ; 1 study<sup>19</sup>). One RCT assessed disease-specific quality of life using the Rhinoconjunctivitis Quality of Life Questionnaire.<sup>22</sup> However, only the results between the active treatments and placebo were reported. The data on the standard-dose and double-dose INCS were not reported.

### Heterogeneity

Most meta-analyses had low to moderate heterogeneity. However, the heterogeneity of sneezing in the adult population reached a substantial level. The data were pooled from 3 included RCTs.<sup>12,20,22</sup> Two RCTs studied patients with seasonal AR<sup>20,22</sup> and 1 RCT studied patients with perennial AR.<sup>12</sup> When the data from RCT with perennial AR were removed, the  $I^2$  became 0%. The meta-analysis results of the 2 RCTs of seasonal AR also showed no statistical difference between the double-dose and the standard-dose INCS.

### Adverse events

There were 9 RCTs that assessed adverse events.<sup>11,13,14,16,18–22</sup> There were no statistically significant differences between groups on any adverse event including epistaxis, nasal irritation, headache, and pharyngitis. Data are displayed in Table 2.

### Risk of bias in the included studies

In general, included studies had poor quality. All included studies had unclear risks of bias in random sequence generation and allocation concealment. Twenty-three percent had low risk of bias in blinding of outcome assessment. Fifty-four percent had low risk of bias in selective reporting. All included studies had low risk of bias in incomplete outcome data. In summary, the included studies had risks of selection bias, detection bias, and reporting bias whereas they had low risk of attrition bias (Figs. 7 and 8).

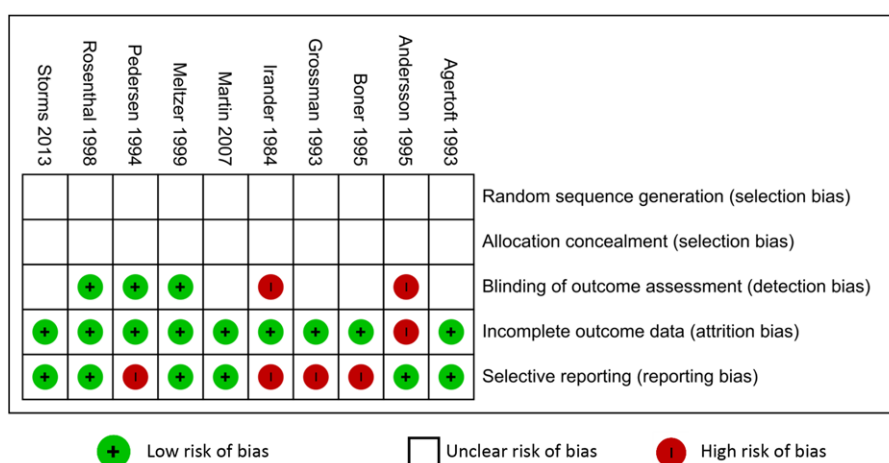
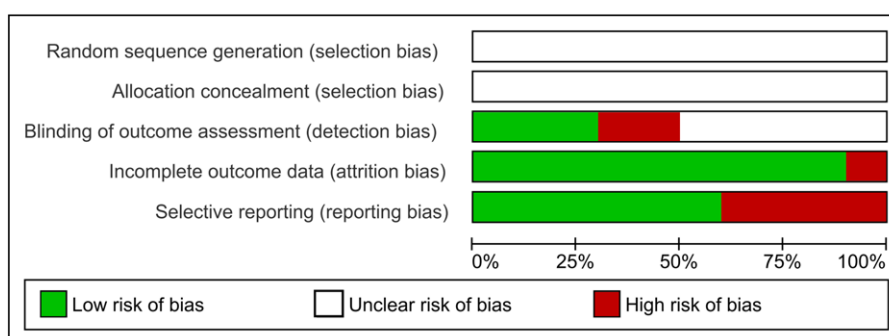
### Discussion

The results of this study showed that the double-dose INCS provided greater clinical responses in adult patients than the standard-dose INCS on nasal symptoms and ocular symptoms. Boger et al.<sup>7</sup> revealed a dose-receptor occupancy relationship by measuring glucocorticoid receptor occupancy in rats. The glucocorticoid receptor occupancy was measured at 1.5 hours after administration of 3 dosages of intravenous (IV) fluticasone propionate (20, 150, and 750 nmol/kg). They found that the glucocorticoid receptor occupancy level correlates with the dosage of fluticasone propionate. Therefore, glucocorticoids bind to glucocorticoid receptors and regulate the gene transcription including: (1) upregulating the anti-inflammatory protein expression in

**TABLE 2.** Adverse events of double-dose intranasal corticosteroids compared to standard dose

| Adverse events   | Included studies                                                                                                                                                                                                                                                                                       | Studies (n) | Patients (n) | Risk ratio (95% CI) | p    |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|---------------------|------|
| Epistaxis        | Agertoft et al. <sup>11</sup> (1993); Grossman et al. <sup>16</sup> (1993); Boner et al. <sup>13</sup> (1995); Meltzer et al. <sup>18</sup> (1999); Storms et al. <sup>21</sup> (2013); Irlander et al. <sup>14</sup> (1984); Martin et al. <sup>22</sup> (2007); Pederson et al. <sup>19</sup> (1994) | 8           | 1515         | 0.79 (0.50–1.26)    | 0.32 |
| Nasal irritation | Grossman et al. <sup>16</sup> (1993); Irlander et al. <sup>14</sup> (1984); Rosenthal et al. <sup>20</sup> (1998)                                                                                                                                                                                      | 3           | 426          | 0.83 (0.52–1.33)    | 0.44 |
| Headache         | Grossman et al. <sup>16</sup> (1993); Boner et al. <sup>13</sup> (1995); Meltzer et al. <sup>18</sup> (1999); Storms et al. <sup>21</sup> (2013); Rosenthal et al. <sup>20</sup> (1998); Martin et al. <sup>22</sup> (2007)                                                                            | 6           | 1453         | 0.93 (0.47–1.84)    | 0.84 |
| Pharyngitis      | Boner et al. <sup>13</sup> (1995); Meltzer et al. <sup>18</sup> (1999); Rosenthal et al. <sup>20</sup> (1998)                                                                                                                                                                                          | 3           | 550          | 1.61 (0.62–4.20)    | 0.33 |

CI = confidence interval.

**FIGURE 7.** Risk of bias summary: each risk of bias item for each included study.**FIGURE 8.** Risk of bias graph: each risk of bias item presented as percentages across all included studies.

the nucleus; and (2) repressing the pro-inflammatory proteins expression in the cytosol.<sup>5</sup> Doubling the standard dosage of INCS, which increases the occupancy of the glucocorticoid receptor, should provide greater clinical effects. This could explain the results of this study, that the double-dose INCS provided greater clinical responses in adult patients than the standard-dose INCS. Although the differences were statistically significant, these beneficial effects were minimal. However, the beneficial effects were

not seen in the pediatric population. Therefore, the clinical utility may be limited.

Ocular adverse events are one of the concerns of the doctors and patients especially when the double-dose INCS is prescribed. None of the included RCTs reported adverse effects on intraocular pressure and lens opacity either in standard-dose or double-dose groups. This is in line with a systematic review by Ahmadi et al.<sup>23</sup> that no clinically relevant impacts on either intraocular pressure or lens opacity

were found in 10 randomized controlled trials. In addition, there were no major adverse events reported in the included RCTs and no differences in minor local adverse events of the double-dose INCS when compared to the standard-dose INCS.

To date, there is no evidence to support the use of combinations of INCS with oral antihistamines,<sup>24-27</sup> decongestants,<sup>28,29</sup> or leukotrienes receptor antagonists.<sup>30</sup> Thus, the double-dose INCS should be considered as an option for treating adult patients with AR who have an inadequate response to the standard dose. Patients with seasonal AR and patients with perennial AR may benefit from the double dose of INCS on nasal and ocular symptom improvements. The role of double-dose INCS has been mentioned in a flow diagram in the ARIA 2008.<sup>1</sup> Increasing the INCS dosage is suggested when the standard treatments fail to improve symptoms of the patients with persistent or moderate to severe AR. The definite diagnosis, drug compliance, concurrent respiratory tract infection, and other causes should be reviewed. However, there were no details, level of evidence, and grade of recommendation regarding this suggestion. Moreover, the double dose of INCS has not been mentioned by the American Academy of Otolaryngology–Head and Neck Surgery<sup>2</sup>

and the International Consensus Statement on Allergy and Rhinology.<sup>31</sup>

There were several limitations in this study. The included studies generally had poor descriptions of methodology. They did not describe random sequence generation or allocation concealment. Most studies did not blind doctors and patients. The standard deviations of several studies were not reported and could not be imputed. There was insufficient information regarding the validation of the total nasal and ocular symptom scores used by most studies. Therefore, the confidence in the results was limited. Nevertheless, the strength of this study was the statistical power of these meta-analyses from a large number of patients.

## Conclusion

Double-dose INCSs showed better improvement in nasal and ocular symptoms in adult patients with AR when compared to the standard dose. The dosage of INCS may be doubled to control nasal and ocular symptoms in adult patients with AR who have inadequate response to the standard dose. These beneficial effects were not observed in the pediatric population. There were no differences in adverse events between the double dose and standard dose of INCS. 🌐

## References

- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160.
- Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015;152(1 Suppl):S1–S43.
- Snidvongs K, Thanaviratnanich S. Update on intranasal medications in rhinosinusitis. *Curr Allergy Asthma Rep*. 2017;17:47.
- Lee SH. Mechanisms of glucocorticoid action in chronic rhinosinusitis. *Allergy Asthma Immunol Res*. 2015;7:534–537.
- Mullol J, Obando A, Pujols L, Alobid I. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol Allergy Clin North Am*. 2009;29:657–668.
- Boger E, Evans N, Chappell M, et al. Systems pharmacology approach for prediction of pulmonary and systemic pharmacokinetics and receptor occupancy of inhaled drugs. *CPT Pharmacometrics Syst Pharmacol*. 2016;5:201–210.
- Boger E, Ewing P, Eriksson UG, et al. A novel in vivo receptor occupancy methodology for the glucocorticoid receptor: toward an improved understanding of lung pharmacokinetic/pharmacodynamic relationships. *J Pharmacol Exp Ther*. 2015;353:279–287.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. London, UK: The Cochrane Collaboration; 2011. <https://training.cochrane.org/handbook>. Accessed August 24, 2018.
- Review Manager (RevMan) [computer program]. Version 5.1.6. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.
- Agertoft L, Wolthers OD, Fuglsang G, Pedersen S. Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents. *Pediatr Allergy Immunol*. 1993;4:152–156.
- Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. *Rhinology*. 1995;33:18–21.
- Boner A, Sette L, Martinati L, Sharma RK, Richards DH. The efficacy and tolerability of fluticasone propionate aqueous nasal spray in children with seasonal allergic rhinitis. *Allergy*. 1995;50(6):498–505.
- Irander K, Geterud A, Lindqvist N, Pipkorn U. A single blind clinical comparison between 2 preparations of budesonide in the treatment of seasonal allergic rhinitis. *Clin Otolaryngol Allied Sci*. 1984;9:235–241.
- Creticos P, Fireman P, Settupane G, Bernstein D, Casale T, Schwartz H. Intranasal budesonide aqueous pump spray (Rhinocort Aqua) for the treatment of seasonal allergic rhinitis. *Rhinocort Aqua Study Group. Allergy Asthma Proc*. 1998;19:285–294.
- Grossman J, Banov C, Bronsky EA, et al. Fluticasone propionate aqueous nasal spray is safe and effective for children with seasonal allergic rhinitis. *Pediatrics*. 1993;92:594–599.
- Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 1998;81:128–134.
- Meltzer EO, Berger WE, Berkowitz RB, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1999;104:107–114.
- Pedersen B, Larsen BB, Dahl R, Hedbys L, Mygind N. Budesonide powder administration for the treatment of grass-pollen-induced allergic rhinitis. *Allergy*. 1994;49:855–860.
- Rosenthal R, Berger W, Bronsky E, et al. Tri-Nasal triamcinolone acetonide nasal spray 200 and 400 micrograms qd versus placebo and Nasacort triamcinolone acetonide nasal aerosol 440 micrograms qd in patients suffering from seasonal allergic rhinitis during the grass season. *Am J Rhinol*. 1998;12:427–433.
- Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2013;111:408–414.e1.
- Martin BG, Ratner PH, Hampel FC, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. *Allergy Asthma Proc*. 2007;28:216–225.
- Ahmadi N, Snidvongs K, Kalish L, et al. Intranasal corticosteroids do not affect intraocular pressure or lens opacity: a systematic review of controlled trials. *Rhinology*. 2015;53:290–302.
- Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Khattiyawittayakun L, Snidvongs K. Effects of H1 antihistamine addition to intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2018 Jun 19. doi: 10.1002/alr.22166.
- Anolik R; Mometasone Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:264–271.
- Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy*. 2006;36:676–684.
- Kim CH, Kim JK, Kim HJ, et al. Comparison of intranasal ciclesonide, oral levocetirizine, and combination treatment for allergic rhinitis. *Allergy Asthma Immunol Res*. 2015;7:158–166.
- Khattiyawittayakun L, Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Effects of decongestant addition to intranasal corticosteroid for chronic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2018 Jul 28. doi: 10.1002/alr.22193.
- Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. 2011;127:927–934.
- Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy*. 2004;34:259–267.
- Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8:108–352.