Background: There is no consensus regarding the effects on growth velocity of intranasal topical corticosteroid (ITC) use in children. The objective of this study was to determine whether ITC use reduces growth velocity in children with allergic rhinitis (AR).

Methods: A literature search of the National Center for Biotechnology Information PubMed, EMBASE, SCOPUS, and Cochrane databases from January 1, 1988 to October 7, 2013. The study selection was composed of randomized clinical trials investigating ITC for treatment of AR in children (age <18 years of age) with appropriate controls. Studies must have included interval change in growth as an outcome. Two authors independently extracted data and assessed study quality. Eligible studies were pooled using a random-effects approach.

Results: Eight studies with 755 participants from 3 countries provided data for the meta-analysis (knemometry, n = 342 participants; stadiometry, n = 413 participants). Study duration ranged from 2 to 4 weeks for trials evaluating knemometry outcomes, and 12 months for trials evaluating stadiometry outcomes. Age of participants ranged from 3 to 12 years. The pooled standardized mean difference showed that among studies using knemometry, mean growth was statistically significantly lower among children using ITC vs placebo (−0.223 mm/week; 95% confidence interval [CI], −0.429 to −0.017; p < 0.034). The pooled standardized mean difference showed that among studies using stadiometry, there was no significant growth difference among children using ITC vs placebo (−0.053 cm/year; 95% CI, −0.491 to 0.385; p = 0.813). The limitations of this study were the difficulty in predicting longer-term or catch-up growth in children.

Conclusion: Meta-analytic pooling of trials suggest that short-term ITC for the treatment of AR in children may decrease short-term growth velocity using knemometry; however, the effect on longer-term growth velocity as measured by stadiometry is unclear. © 2014 ARS-AAOA, LLC.

Key Words: allergic rhinitis; inhaled glucocorticoids; nasal spray; nasal inhaler; glucocorticoid; fluticasone; budesonide; beclomethasone; androstadienes; steroids; budesonide

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nonprescription drugs advisory committee recently recommended on July 31, 2013 in a vote of 10 to 6 with 2 abstentions that triamcinolone acetonide be switched from prescription to over the counter in children older than 2 years of age. This recommendation was formally approved by the FDA in October 2013. However, there is concern that intranasal corticosteroids, which are well established for the treatment of allergic rhinitis, may in fact be responsible for growth retardation in children through suppression of the hypothalamic-pituitary-adrenal axis. This change of status from prescription to over-the-counter use will likely increase accessibility to young children without necessarily the prior approval of pediatricians. Thus, this meta-analysis is of current interest and importance to clinicians and patients in elucidating the effects of intranasal corticosteroid on growth velocity in children.

Knemometry, which measures linear leg growth with an accuracy of 0.1 mm, is a particularly sensitive and reproducible measure of short-term growth velocity in children. Stadiometry on the other hand, is a useful longer-term measure of growth velocity that measures vertical height from weeks to years. Thus, the detection of potential systemic adverse effects on growth in children can be evaluated in randomized controlled studies that examine short-term (knemometry) or longer-term (stadiometry) growth velocity outcome measures.

Individual trials analyzing the associations between topical nasal corticosteroids and growth velocity in children have not produced conclusive results. Some studies have shown that short-term intranasal corticosteroids have no effect on growth velocity in children, while other trials have shown growth suppression or potential but not statistically significant growth suppression. The objective of this meta-analysis, therefore, is to evaluate the association between intranasal corticosteroids and growth velocity, using knemometry and stadiometry, in children undergoing treatment for allergic rhinitis. To our knowledge, this is the first comprehensive meta-analysis examining this issue.

Materials and methods

Literature search

A quantitative meta-analysis was conducted of the published English literature to broadly investigate the association between intranasal corticosteroid use in children for allergic rhinitis and growth velocity. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was adhered to during the conduct of these quantitative meta-analyses.

In October 2013, 4 large literature sources were searched: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and Scopus. Sources were queried for relevant publications within a 25-year time period ranging from January 1, 1988 through October 7, 2013. An initial electronic search strategy was designed for use in PubMed and then tailored to the other electronic databases in similar fashion. The initial search incorporated use of Medical Subject headings (MeSH) in addition to key text words extracted from relevant titles and abstracts (Table 1). A medical librarian assisted in the development of the search strategies and reviewed them each for accuracy and precision. We reviewed reference lists from retrieved articles and reviews to identify further relevant studies. An abstract review, followed by a full-text article review, was then performed to assess for eligibility for inclusion. The search was restricted to human subjects, age <18 years, English language journals, and randomized controlled trials (RCTs). Expert guidance was sought to locate any other trials not identified in the database search and potential unpublished trials. The title review then eliminated any studies where the indication for topical steroids was any diagnosis other than allergic rhinitis. The systematic review was planned, conducted, and reported in adherence to standards of quality for reporting meta-analyses.

Study selection

This meta-analysis considered all RCTs investigating topical nasal steroids for treatment of allergic rhinitis in children (age <18 years of age). To meet inclusion criteria,
the trials had to include (1) an intervention group that received treatment with topical nasal steroids, and (2) a control group in which an appropriate placebo treatment was applied. Crossover trials and RCTs considering multiple different intranasal steroids independently were considered acceptable so long as an appropriate placebo treatment was applied to all groups equally. Crossover trial methodology is particularly useful in evaluating growth velocity in children since participants can serve as their own controls. This is potentially an important issue since comparing growth velocity among children with a variety of ages and among different stages of puberty may be challenging. Trials where participants were given short-term oral corticosteroids (<7 days per incident) for asthma exacerbations in children were included. Patients could not have had exposure to intranasal steroids prior to study commencement unless an adequate washout period was described in the RCT.

**Outcome measures**

The primary outcome in this meta-analysis was mean growth velocity, as measured by stadiometry or knemometry, in children, following administration of intranasal steroids or placebo for allergic rhinitis. Any length of follow-up was considered acceptable.

**Quality assessment**

Two authors (J.S. and D.J.M.) independently assessed study quality using the Centre for Evidence Based Medicine levels of evidence for primary research question (http://www.cebm.net).

**Data extraction**

Two reviewers (J.S. and D.J.M.) independently extracted and cross-checked data from all RCTs included in the meta-analysis. For trials that used stadiometry and knemometry measurements, variables extracted included intranasal steroid type, daily dosing, baseline height, height at termination of the trial, and mean growth velocity parameters. When available, standard errors and standard deviations of growth parameters were reported.

**Statistical analysis**

Two independent meta-analyses were conducted evaluating the association of intranasal steroids and (1) knemometry and (2) stadiometry. Among RCTs and crossover trials that evaluated the clinical effects and/or outcomes of the same intranasal steroid at multiple doses, only the participants using the highest daily dose were included in the analysis. Sample size for crossover trials was calculated by adding the total number of participants treated with each individual topical intranasal corticosteroid, in addition to the number of participants in the control group. This is a conservative approach that underweights crossover trials. Meta-analyses were performed using the Comprehensive Meta-analysis program version 2 (Englewood, NJ). For each meta-analysis, the standardized difference in means was calculated as the mean difference in growth velocity for treatment effect using random effects modeling based on the crude, study-specific growth velocities and 95% confidence intervals. Forest plots were then constructed for (1) knemometry and (2) stadiometry. Study heterogeneity was assessed by using the $I^2$ statistic, which measures the degree of inconsistency. Two-sided $p < 0.05$ was considered statistically significant.

**Results**

**Literature results**

The results of our literature search are summarized in Figure 1. After using the outlined literature search strategy, 623 records were identified. Of these, 454 records were initially excluded based on title review, the vast majority being nonhuman studies (397 articles). Many of the remaining records were irrelevant to the primary research question (102 articles), were nonrandomized trials (eg, systematic and narrative reviews, clinical guidance documents, commentaries, letters, and press releases, or had no control/placebo group) (8 articles). This left 59 articles that were assessed in more detail for eligibility. Nearly half of these included adult participants only (27 articles). Of the remaining articles, 10 studies met the inclusion criteria. Two studies did not report sufficient data on growth velocity to be included. The remaining articles were then included in the meta-analyses for stadiometry and knemometry (N = 4). Eight trials were included and the summary characteristics appear in Table 2.

**Clinical trial characteristics**

The characteristics of the included studies are listed in Tables 2 to 4. Eight studies with 755 participants from 3 countries provided data for the meta-analysis (knemometry meta-analysis, n = 342 participants; stadiometry meta-analysis, n =413 participants). Study duration ranged from 2 to 4 weeks for trials evaluating knemometry outcomes, and 12 months for trials evaluating stadiometry outcomes. Age of participants ranged from 3 to 12 years. Regarding controls/placebos, all trials were double-blinded and used placebo insufflators. Three trials were designed using double-blinded randomized crossover methodology, and the remaining 5 trials were designed using double-blinded parallel group methodology. Two trials evaluated stadiometry growth velocity of 2 different intranasal corticosteroid preparations, each of which was included in the analysis. Intranasal steroids examined with stadiometry outcomes included Fluticasone 200 mg/day, budesonide 64 μg/day, and mometasone 100 μg/day. Intranasal...
steroids examined with knemometry outcomes included Budesonide (200 μg/day and 400 μg/day), triamcinolone (100 μg/day and 220 μg/day), fluticasone 200 mg/day, and mometasone (100 μg/day and 200 μg/day).

Meta-analysis 1: knemometry

Figure 2 shows a forest plot of the individual and overall associations between intranasal steroid use and knemometry. Among the 4 studies using knemometry as an outcome
TABLE 2. Characteristics of studies included in meta-analysis

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Location</th>
<th>Age range (years)</th>
<th>n</th>
<th>Intranasal steroid</th>
<th>Daily dose</th>
<th>Intranasal steroid duration</th>
<th>Quality score</th>
<th>Study design</th>
<th>Growth outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. (^5) (2002)</td>
<td>USA</td>
<td>3.5–9</td>
<td>83</td>
<td>Fluticasone</td>
<td>200 mg</td>
<td>1 year</td>
<td>1</td>
<td>RCT</td>
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<tr>
<td>Murphy et al. (^21) (2006)</td>
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<td>168</td>
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<td>USA</td>
<td>6–9.5</td>
<td>80</td>
<td>Mometasone</td>
<td>100 μg</td>
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<td>Stadiometry</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.

TABLE 3. Evidence table of stadiometry studies included in meta-analysis

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Location</th>
<th>Age range (years)</th>
<th>n</th>
<th>Intranasal steroid</th>
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</tr>
</tbody>
</table>

Values are mean ± SE or mean ± SD, as indicated. SD = standard deviation; SE = standard error.

measure (Table 3), the overall effect showed that mean growth velocity was statistically significantly lower among children using intranasal steroids vs placebo (−0.223 mm/week; 95% confidence interval [CI], −0.429 to −0.017; p < 0.034). None of the individual studies demonstrated a statistically significant difference in growth velocity on knemometry measurement. Heterogeneity was low across trial findings (I^2 = 8.75%, p = 0.36).

**Meta-analysis 2: stadiometry**

Figure 3 shows a forest plot of the individual and overall associations between intranasal steroid use and stadiometry. Among the 4 studies using stadiometry as an outcome measure (Table 4), the overall effect showed that there was no significant growth velocity difference among children using intranasal steroids vs placebo (−0.053 cm/year; 95% CI, −0.491 to 0.385; p = 0.813). However, effects were highly heterogeneous across studies (I^2 = 78.51%, p = 0.003), with individual trials results having inconsistent growth velocities.

**Discussion**

Overall, the meta-analysis demonstrated a significant decrease in mean growth velocity using knemometry measurements among children receiving topical intranasal corticosteroids compared to those receiving placebo, despite the fact that none of the individual knemometry trials demonstrated a statistically significant effect of intranasal steroids on growth velocity. However, the effect on longer-term growth velocity, as measured by stadiometry, is unclear since heterogeneity was large and statistically significant, with individual trial results demonstrating inconsistent growth velocity parameters. The pooled meta-analysis knemometry growth velocity findings are concerning given the widespread use of intranasal corticosteroid in children with allergic rhinitis.

This analysis adds to existing reviews and provides the first comprehensive meta-analysis on this important topic. Important points that can be drawn from this analysis include (1) even short-term intranasal corticosteroid use in children may have deleterious effects on short-term
TABLE 4. Evidence table of knemometry studies included in meta-analysis

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Intranasal steroid (daily dose)</th>
<th>Growth velocity (mm)</th>
<th>n</th>
<th>Growth velocity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolthers and Pedersen (1994)</td>
<td>14</td>
<td>Budesonide (200 μg)</td>
<td>0.27 ± 0.20 SD(^a)</td>
<td>10</td>
<td>0.34 ± 0.20 SD(^a)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Budesonide (400 μg)</td>
<td>0.22 ± 0.19 SD(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skoner et al. (2003)</td>
<td>49</td>
<td>Triamcinolone (110 μg)</td>
<td>0.37 ± 0.42 SE(^a)</td>
<td>49</td>
<td>0.47 ± 0.06 SE(^a)</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Triamcinolone (220 μg)</td>
<td>0.32 ± 0.42 SE(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Fluticasone (200 μg)</td>
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</tr>
<tr>
<td>Agertoft and Pedersen (1999)</td>
<td>22</td>
<td>Mometasone (100 μg)</td>
<td>0.58(^b)</td>
<td>22</td>
<td>0.35(^b)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Mometasone (200 μg)</td>
<td>0.48 ± 0.304 SE(^b)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Budesonide (400 μg)</td>
<td>0.37 ± 0.302 SE(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gradman et al. (2007)</td>
<td>53</td>
<td>Fluticasone (100 μg)</td>
<td>0.41 ± 0.06 SD(^a)</td>
<td>53</td>
<td>0.43 ± 0.06 SD(^a)</td>
</tr>
</tbody>
</table>

Values are mean ± SE or mean ± SD, as indicated.
\(^a\)Values are millimeters per week (mm/week).
\(^b\)Values are millimeters every 2 weeks (mm/2 weeks).
SD = standard deviation; SE = standard error.

FIGURE 2. Forest plot of knemometry growth velocity effect size for intranasal corticosteroids.

measures of growth, and (2) it is unclear whether these effects translate into long-term suppression of growth. An advantage of assessing knemometry to evaluate the effect of intranasal steroids on growth include the relatively easy ability to observe short periods of growth in children, which then enables investigators to design trials using crossover designs and randomized controlled clinical trials. To date, there has only been 1 systematic review evaluating topical nasal steroids for intermittent and persistent allergic rhinitis in children.\(^{25}\) This study did not demonstrate or report adverse events in any of the 3 trials, finding that the data analysis was flawed in 2 of the trials and incomprehensible in the third.\(^{25}\)

Topical intranasal corticosteroids act directly on the nasal mucosa to produce optimal effects, but older trials have shown that dexamethasone, beclomethasone, and betamethasone may induce moderate adrenal suppression.\(^{26–28}\) The primary response of corticosteroids on the hypothalamic pituitary axis is negative feedback caused by suppression of corticotrophin-releasing hormone and adrenocorticotropic hormone levels, resulting in decreased cortisol secretion.\(^{29}\) While intranasal steroids provide direct delivery to the nasal mucosa, much of the medication dose is in fact transported into the gastrointestinal tract through mucociliary clearance, which must then become inactivated by first-pass hepatic metabolism.\(^{30}\)
Absorption into systemic circulation may occur through airway or gastrointestinal pathways, which may be increased with formulations with high water solubility such as budesonide in contrast to formulation with high lipophilic properties such as mometasone or fluticasone. In ascending order of increased growth suppression in children, high-dose budesonide, fluticasone, triamcinolone, and mometasone, may demonstrate decrease growth velocity by knemometry measurement. However, in contrast, prior pharmacokinetic and pharmacodynamics research have shown that intranasal fluticasone and mometasone are actually predicted to have the least short-term growth suppression effects compared to triamcinolone and budesonide intranasal preparations. Possible differences in bioavailability, with mometasone and fluticasone having the lowest systemic bioavailability, may be contributing factors. Our results may indicate that, despite differences in bioavailability, different intranasal corticosteroid preparations may vary in actual growth suppression potential in children.

Suppression of growth in children may occur through any of several potential mechanisms. These include decreased release of growth hormone, inhibition of insulin-like growth factor 1 activity, blunting of pulsatile growth hormone release, downregulation of growth hormone receptor expression, and suppression of collagen synthesis and adrenal androgen production. However, there appears to be no evidence of other systemic effects of intranasal corticosteroids in children for the treatment of allergic rhinitis, including electrolyte imbalances, alterations in protein, lipid, or carbohydrate metabolism, or alterations in differential white blood cell counts. Short-term evaluation of mean growth velocity using knemometry may in fact be a more sensitive indicator of systemic corticosteroid effects than traditional measures of hypothalamic-pituitary axis suppression.

Intranasal corticosteroid preparations may be more likely to cause growth suppression with twice-daily vs once-daily administration or with formulations that have a more complete first-pass hepatic inactivation. Our data support this hypothesis, with higher-dose corticosteroids causing consistently more growth velocity suppression by knemometry measurement. While our meta-analysis demonstrated decreases in short-term growth velocity, intranasal steroids may in fact have no significant effect on final adult height. Stadiometry studies that span at least 12 months may in fact provide the most clinically useful information about the association of growth velocity and intranasal corticosteroids.

The strengths and limitations of this study should be considered. First, only a relatively small number of RCTs were available for analysis. Nevertheless, the individual trials analyzing knemometry measurements were fairly consistent in demonstrating decreased growth velocity among children using intranasal topical corticosteroids compared to placebo; however, none of the individual trial analyses showed statistical significance. The consistency of the pooled analysis among the knemometry trials and the individual study results adds credibility to the pooled results. However, the pooled meta-analysis among the stadiometry trials did not provide any inference due to substantial heterogeneity in treatment effects. We could have taken advantage of including nonrandomized or uncontrolled studies in order to acquire more data. However, we chose systematically to choose only RCTs in order to select trials that were of high quality with strong methodology.

Growth evaluation by knemometry provides accurate and precise measurements of short-term lower leg growth is less prone to systematic observer variation than stadiometry, but does not provide insight into longer-term growth rates. A longer duration of
administration, however, was analyzed using stadiometry. Difficulty arises in evaluating the growth of children, since growth occurs in spurts, interspersed with periods of low growth velocity. While the individual studies were all careful about matching the ages of the treatment and control groups, variability among the ages of children between the individual studies may affect the results. The heterogeneity among the stadiometry studies may at least partially be explained by the above, in addition to differences in individual trials among treatment and placebo arms with respect to baseline height among children, small differences in the proportion of children diagnosed with asthma who may have required rescue corticosteroid medications, differences in the proportion of children advancing developmentally with respect to puberty, and differences in compliance among intranasal corticosteroid preparations. Additional difficulty arises in predicting longer-term growth velocity in children. Even consistent knemometry measurements by clinicians over a 4-month period have been shown to have variable predictive value in predicting overall 6-month growth velocity among children. Limitations of individual studies in the analysis include the occasional need to give limited duration oral corticosteroids for acute asthma exacerbations; however, this likely did not affect the standardized difference in means of growth velocity since all trials were randomized and the need for rescue oral corticosteroids was likely balanced between intervention and placebo groups.

Timing of intranasal corticosteroid administration may be an important consideration to preventing adverse effects on growth velocity. Since growth hormone secretion in prepubertal children is pulsatile and foremost nocturnal, absorption of exogenous corticosteroids during those times may have increased effect on growth suppression and growth hormone release. Timing of intranasal corticosteroids in the morning may partially mitigate this effect and should be considered an important factor in designing future RCTs assessing growth velocity, in addition to assessing Tanner stage at fixed timed intervals throughout the study duration, when evaluating potential confounders. Finally, the long-term growth outcomes, overall lifetime reduction in growth velocity, and bearing on final adult height in children using intranasal corticosteroids are not well elucidated.

Conclusion

Our findings suggest that short-term intranasal corticosteroids for the treatment of allergic rhinitis in children may decrease short-term growth velocity, as measured by knemometry. Thus, we advocate that children using intranasal corticosteroids should be monitored carefully by pediatricians. Potential adverse effects on growth vs improvement in symptoms of allergic rhinitis must be carefully assessed. When intranasal corticosteroids are selected, the lowest effective dose to achieve the desired clinical outcome should be used.6

References


Topical intranasal corticosteroids and growth velocity


UPCOMING MEETING ANNOUNCEMENT 2015

The 16th World Congress of Rhinology, combining the 34th ISIAN meeting (International Society of Inflammation and Allergy of the Nose), with the 16th IRS meeting (International Rhinologic Society) will be held in Sao Paulo, Brazil, April 30th–May 2nd 2015, under the leadership of Aldo Stamm, M.D. Pre and post congress tours are planned and the meeting will build on Dr. Stamm’s prior reputation for outstanding international rhinology meetings. For more information, please go to http://www.rhinology2015.com/
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