Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis

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CRD summary
This generally well-conducted review compared inhaled corticosteroids and placebo in infants or pre-school children with recurrent wheezing or asthma. It showed that inhaled corticosteroids were associated with fewer asthma/wheezing exacerbations, a lower rate of withdrawals and better clinical and functional improvement than placebo. Despite a relatively limited search, the conclusions appear likely to be reliable.

Authors' objectives
To compare the efficacy of inhaled corticosteroids compared to placebo in infants and pre-school children with recurrent wheezing or asthma.

Searching
MedLine, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to 2008. Search terms were reported. There were no language restrictions. Studies reported only as an abstract were excluded.

Study selection
Randomised controlled trials (RCT) were considered for inclusion. Infants (0 to 23 months) or pre-school children (two to five years) with a clinical diagnosis of wheezing or asthma for at least six months before study entry were examined. The intervention was use of inhaled corticosteroids delivered via metered-dose inhaler or nebulizer, compared to placebo. The primary eligible outcome was asthma/wheezing exacerbations (defined as aggravation of symptoms that required systemic corticosteroid use). Secondary outcome measures were discontinuation because of asthma/wheezing exacerbations, mean change from baseline in pulmonary function (peak expiratory flow and forced expiratory volume in 1 second (FEV1)) and mean change in albuterol use from baseline.

Two reviewers independently evaluated the studies for inclusion.

Twenty-nine studies were included. The number of children in each study ranged from three to 481; 11 studies had over one hundred children. Age ranged from three to 48 months. Three types of inhaled corticosteroids were studied. Therapy duration ranged from four to 36 weeks; 18 trials lasted at least 12 weeks.

Assessment of study quality
Two authors independently evaluated methodological quality using the Jadad five-point scale of adequacy of randomization, blinding and handling of withdrawals and dropouts.

Data extraction
Two reviewers extracted data independently. Data was used to calculate relative risks (RR), standardised (SMD) or weighted mean differences (WMD), with 95% confidence interval (CI).

Methods of synthesis
Pooled relative risks and standardised mean differences or weighted mean differences, with corresponding 95% CI, were calculated using a fixed-effect meta-analysis (where there was heterogeneity); where there was evidence of statistically significant heterogeneity (I²>40%), a random-effects model was used. Number needed to treat (NNT) was calculated for dichotomous outcomes with statistically significant results.

Sensitivity analysis of asthma/wheezing exacerbations was performed for the following factors: disease (wheeze versus asthma), age (<24 months versus two to five years), atopic status (>50% of children with personal and/or parental atopy characteristics versus non-atopic), quality assessment (Jadad score <4 versus ≥4), inhaled corticosteroids delivery (metered-dose inhaler versus nebulizer), inhaled corticosteroids choice (buticasone versus fluticasone) and study duration (<12 versus ≥12 weeks). Results were compared using the interaction test.
**Results of the review**

Twenty-nine RCTs were included in the review (3,592 children). Jadad quality score ranged from 2 to 5.

**Asthma/wheezing exacerbations:** Sixteen studies reported this outcome (2,805 children). Inhaled corticosteroids was associated with lower incidence of asthma/wheezing exacerbations compared to placebo (RR 0.59, 95% CI 0.52 to 0.67, NNT=7). Test for heterogeneity was non significant.

**Secondary outcomes:** A lower rate of withdrawals because of asthma/wheezing exacerbations was reported in patients who took inhaled corticosteroids (RR 0.52, 95% CI 0.43 to 0.63). Statistical heterogeneity was non significant. A significant decrease in mean change from baseline symptom score in patients who took inhaled corticosteroids (SMD: 0.93, 95% CI 0.49 to 1.37) was found. Heterogeneity was statistically significant. Other outcomes with significant differences were: mean change from baseline in albuterol use (SMD 0.63, 95% CI 0.30 to 0.63), FEV1 (WMD 0.07L, 95% CI: 0.05 to 0.09) and peak expiratory flow (WMD 13.8L/minute, 95% CI 5.34 to 22.4). Heterogeneity was statistically significant only in mean change from baseline in albuterol use.

**Authors’ conclusions**

Inhaled corticosteroids were useful in reducing exacerbations and withdrawals caused by exacerbations in infants and pre-school children with persistent wheeze/asthma. They also improved clinical scores, functional measurements and reduced albuterol use when compared to placebo in children of five years or less.

**CRD commentary**

This review addressed a well-defined question in terms of patients, interventions, outcomes and study design. Only two relevant databases were searched and no attempts were made to identify unpublished studies, which increased risk of publication bias. Efforts to minimise other biases and errors were made by not using language restrictions and independently extracting data and evaluating quality.

Characteristics of the included studies were presented clearly and methods used to pool the results were appropriate. Proper methods were used to explore heterogeneity. The author’s conclusions accurately reflected the results of the review and, despite a somewhat limited search, appear likely to be reliable.

Both authors had financial ties with a number of pharmaceutical companies.

**Implications of the review for practice and research**

**Practice:** The authors stated that inhaled corticosteroids should be used in infant/ preschoolers with persistent wheeze/asthma.

**Research:** The authors did not state implications for further research.

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