EFFECTIVENESS OF LONG TERM THERAPY OF INHALED STEROIDS IN CHILDHOOD ASTHMA: A SYSTEMIC REVIEW
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Abstract
Asthma exacerbations are a common and important cause of attendance at emergency departments and subsequent hospital admissions. This systematic review aimed to evaluate the effectiveness of long term therapy of inhaled steroids in childhood asthma. A search of PubMed (Medline) from January 1996 through February 2021 by using the keywords inhaled steroids in childhood asthma, identified potential studies. All randomized controlled trials and clinical trials of prophylactic inhaled steroid therapy for childhood asthma that included data on clinical outcomes (symptoms improvement and concomitant drug use) or laboratory outcomes (peak expiratory flow rate PEFR and (or) forced expiratory volume in first second FEV1) were included. Studies of children (≤18 years old) with mild-to-moderate chronic or persistent asthma will be included. Results: In total, 15 of 116 studies met the inclusion criteria. Inhaled corticosteroids (ICS) versus placebo (3 studies): ICS shows good control on bronchial asthma by ratio (66.7%) and there was no improvement by placebo. ICS versus mast cell stabilizer (2 studies): by ICS there was better control of asthma, lower of airway hyperreactiveness, decrease risk for hospitalization in comparing to mast cell stabilizers by ratio of (66.7%). ICS versus LTRA (Montelukast) (3 studies): by ICS better control of symptoms, modified exacerbation risk, improvement of pulmonary function in comparing to LTRA by ratio of (66.7%). ICS versus OCS (2 studies): more rapid clinical improvement results by OCS (50%), more improvement in the inflammatory markers by ICS (50%), reduction in rescue medication in both groups (100%). ICS alone (3 studies): good control of asthma including exercise asthma (66.7%). This Research concluded that the prophylactic inhaled steroids are more effective compared to placebo, mast cell stabilizer drugs and leukotriene receptor antagonist. ICS improving both clinical and laboratory outcomes in childhood asthma.

Keywords: Asthma, inhaled steroid, clinical trial, randomized controlled trial.

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Introduction
Asthma is one of the most chronic disorders in children, it begins in early life, before the age of 6 many children wheeze, but only 40% of these develop asthma (Wim M. van Aalderen 2012). Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment in adults and children. They remain the most effective anti-inflammatory drugs for the treatment of persistent asthma (Wim M. C et al 2011).

Treatment with ICS has decreased asthma mortality and morbidity (Suissa S et al. 2001). In addition, treatment with ICS reduces symptoms, improves lung function, reduces the degree of bronchial hyperreactiveness (BHR) and reduces the number of exacerbations (Adams NP et al1999, Adams NP et al 2005a, Adams NP et al 2005b). ICS are recommended for the treatment of persistent asthma of all severities in preschool and school age children (J Price 2000).

Materials and Methods
A computer search of the PubMed (MEDLINE) data from January 1996 through February 2021, the keywords inhaled steroids in childhood asthma identified potential studies. All randomized controlled trials and clinical trials of prophylactic inhaled steroid therapy for childhood asthma, only English language publications were retrieved in children with asthma 0 to 18 years of age. Data on the effectiveness of prophylactic inhaled steroid therapy on clinical outcomes (symptom scores, occurrence of cough or wheeze, frequency of concomitant oral steroid or [Beta2-agonist use] and laboratory outcomes (peak expiratory flow rate [PEFR]) were gathered. This Review aims to evaluate the comparative effectiveness of ICS for paediatric asthma. Two types of clinical trials are selected: trials comparing different ICS...
directly and trials comparing ICS with other classes of intervention (eg: LTRA, mast cell stabilizers, OCS or placebo).

**Results**

In total, the MEDLINE search identified 116 studies, of which 15 randomized controlled trials and clinical trials of prophylactic inhaled steroids studies of children (≤18 years old) with mild-to-moderate chronic or persistent asthma. The features of the included studies are described in the following Table. In total, 13682 children were studied in the 15 clinical trials, with study sample sizes ranging from 13 to 11195 children. Thirteen (86.7%) of the trials involved school-aged children, whereas seven (46.7%) involved school and preschool aged children, three (20%) involved infants. Several different inhaled steroids were used as the experimental treatment, with variation also in the dose and route of delivery. The median duration of steroid use was 32.2 weeks (range, 1 to 192 weeks).

In fifteen studies were included, **ICS versus placebo (3 studies):** two (66.7%) of studies show improvement of clinical symptoms and good control of asthma by ICS, two (66.7%) show improvement of airway responsiveness by ICS, and one (33.3%) show improvement of both clinical symptoms and airway responsiveness by ICS but no effect by Placebo. **ICS versus Mast cell stabilizer (DSCG, cromolyn sodium or nedocromil) (6 studies):** Four studies (66.7%) show more improvement of clinical symptoms, good asthma control and decreased asthma exacerbation by ICS, two studies (33.3%) show better health status, better Life quality, more symptom-free days and improvement of airway responsiveness by ICS, one study (16.7%) show good effect on inflammatory markers by ICS and one study (16.7%) show the ICS and Mast cell stabilizer have the same effect on rescue medication. One study found small and transient reduction in growth velocity in ICS group comparing to mast cell stabilizer group.

**ICS versus LTRA (Montelukast) (3 studies):** two studies (66.7%) show more improvement of clinical symptoms, better pulmonary function and improvement of inflammatory markers by ICS, one study (33.3%) shows decrease of asthma exacerbation more by ICS.

**ICS versus OCS (2 studies):** one study (50%) shows there was more rapid clinical improvement results by OCS in comparing to ICS and other study shows (50%) there was more improvement in the inflammatory markers by ICS in comparing to OCS, reduction in rescue medication in both groups (100%). ICS without comparison with other drugs (3 studies): two studies (66.7%) show good control on asthma symptoms, one study (33.3%) shows improvement in airway responsiveness by ICS, one study (33.3%) shows improvement in pulmonary function by ICS.

**Table:** Features of the randomized controlled trials and clinical trials of prophylactic inhaled steroids in childhood asthma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No.</th>
<th>Range of Age in years</th>
<th>ICS versus others</th>
<th>daily</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert K</td>
<td>P</td>
<td>58</td>
<td>6-16</td>
<td>Flonisolide 27 pt : OCS 28 pt</td>
<td>4 inh.(1mg) bid</td>
<td>1w</td>
</tr>
<tr>
<td>A Baki</td>
<td>P</td>
<td>43</td>
<td>7-17</td>
<td>4 groups BUD:Placebo: nedocromil: Salmeterol</td>
<td>200g 2x puffs bid of BUD</td>
<td>3w</td>
</tr>
<tr>
<td>BeyzaPoplata C Direkwattanacha</td>
<td>RC</td>
<td>13</td>
<td>7-17</td>
<td>FP 39 pt.: OCS 41 pt.</td>
<td>2000 ug/d neb.</td>
<td>1w</td>
</tr>
<tr>
<td>Kevin R</td>
<td>P</td>
<td>335</td>
<td>2-6</td>
<td>BUD neb.160 pt.x: cromoly. 167 pt.</td>
<td>0.5 mg once or bid</td>
<td>52w</td>
</tr>
<tr>
<td>Nulma S</td>
<td>RC</td>
<td>102</td>
<td>5-14</td>
<td>BDP</td>
<td>500-750ug/d/ spacer</td>
<td>48w</td>
</tr>
<tr>
<td>Prytilae</td>
<td>P</td>
<td>60 pt.+ 17 H</td>
<td>5-10</td>
<td>BUD:DSCG</td>
<td>400ug bid/1m then 200 ug bid/5m</td>
<td>24w</td>
</tr>
<tr>
<td>Robert S</td>
<td>crossover</td>
<td>144</td>
<td>6-17</td>
<td>FP:Mont.</td>
<td>100 ug Diskus bid</td>
<td>16 w</td>
</tr>
<tr>
<td>Ronina A Covar</td>
<td>P</td>
<td>285</td>
<td>6-14</td>
<td>FP:FP+Salmeterol:Mont.</td>
<td>100ug bid</td>
<td>48 w</td>
</tr>
<tr>
<td>RJ Chavasse</td>
<td>P</td>
<td>52</td>
<td>3-12m</td>
<td>FP:Placebo</td>
<td>150ug bid MDI</td>
<td>12 w</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R.J Adams</th>
<th>P</th>
<th>11195</th>
<th>3-15</th>
<th>ICS: Cromolyn</th>
<th>NA</th>
<th>48w</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Zielen</td>
<td>P</td>
<td>82</td>
<td>&lt; 36 m</td>
<td>BUD neb.: DSCG</td>
<td>0.5 mg / 2ml bid</td>
<td>12 w</td>
</tr>
<tr>
<td>Stanley Szeffler</td>
<td>P</td>
<td>1041</td>
<td>5-12</td>
<td>BUD: Nedocromil: Placebo</td>
<td>200 ug bid</td>
<td>192w</td>
</tr>
<tr>
<td>Stanley J</td>
<td>crossover</td>
<td>126</td>
<td>6-17</td>
<td>FP: Mont.</td>
<td>100 ug bid</td>
<td>8 W</td>
</tr>
<tr>
<td>S La Grutta</td>
<td>crossover</td>
<td>65</td>
<td>5-12</td>
<td>BDP</td>
<td>400 ug bid 2w/12 w 800 ug once or 400 ug bid</td>
<td>14 w</td>
</tr>
</tbody>
</table>


Discussion
This systematic review of the published literature, demonstrates the effectiveness of prophylactic inhaled steroids in childhood asthma. A marked improvement in all clinical and laboratory parameters in the inhaled steroid group compared with the mast cell stabilizer drugs, LTRA or placebo groups was noted in the majority of studies. The review was used randomized, clinical trials, double blind controlled trials. The reviewed studies were not homogeneous because trials differed by source population, patient age, and asthma severity, as well as by type, dose, and duration of inhaled steroid. Despite these differences, the results in the inhaled steroid group were consistent, and showed significant improvement in the symptoms in comparing to other groups where mast cell stabilizer drugs, LTRA or placebo used. Other important clinical outcomes such as hospital admission or emergency department visits (repeat exacerbation) were studied in only four trials suggested that prophylactic inhaled steroid used reduce the hospitalization and emergency department visits. All adverse effects reported were minor and not sufficient to stop treatment. Specifically, there were no documented serious effects of inhaled steroid therapy in terms of growth, adrenal function, or cataract formation.

Conclusion
Prophylactic inhaled steroids are effective in improving both clinical parameters and peak flow rates in children with asthma. Clinical effectiveness was demonstrated in children with both moderate and severe asthma and across a wide age range after a median duration of therapy of around 34.8 weeks.

Abbreviations
PEFR: peak expiratory flow rate
FEV1: forced expiratory volume in first second.
NO: nitric oxide
LTRA: leukotriene receptor antagonist.
IgE: Immunoglobulin

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