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Research Article

Growth of Children with Persistent Asthma Taking Inhaled Corticosteroids

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Abstract

Background: Growth of children with asthma treated with inhaled corticosteroids (ICS) is usually assessed in randomized clinical trials.

Methods: We conducted a hospital-based observational study to assess the growth of children with asthma. We recruited children with persistent asthma taking ICS and children with intermittent asthma who were not treated with ICS, matched by age. Child's growth was measured by height (cm), height-for-age (stunted: <-2 Z-scores) and growth patterns (catch-up growth, suppressed growth, persistent stunting and normal growth).

Results: Of 323 included patients, 217 had persistent asthma regularly taking ICS and 106 had intermittent asthma. The mean height at time of study was 120.4 ± 16.3 cm and 120.7 ± 16.7 cm in the persistent and intermittent asthma group, respectively (p = 0.89). Nine patients (2.8%) were stunted at time of study; five (2.3%) from the persistent and four (3.8%) from the intermittent asthma group (p = 0.48). Only four patients (two from each group) had suppressed growth pattern (normal birth length, but stunted at time of study). Most of patients who were stunted at birth achieved normal height-for-age at time of study in both groups (93.8% vs. 92.0%, p=1.0). No significant differences were observed between two groups regarding growth pattern.

Conclusions: There is no significant difference in height and growth pattern between children with persistent asthma taking ICS and those with intermittent asthma who were not treated with ICS.

Keywords: *Asthma; Inhaled Corticosteroids; Height-for-Age; Stunting; Growth Pattern*

Introduction

Childhood asthma is a major public health problem in both developing and developed countries. Inhaled corticosteroids (ICS) are currently considered first-line treatment for children with persistent asthma [1]. Numerous studies consistently show clinical benefits of ICS in controlling symptoms, reducing exacerbations and hospitalizations, decreasing airway hyperresponsiveness and airway inflammation, improving pulmonary function, improving quality of life and reducing asthma-related deaths [2-5].

Although ICS are generally considered to be safe and well tolerated in children with asthma, concerns have been raised regarding the potential systemic adverse effects related to long-term use of these drugs, especially the effects on growth [6,7].

Two recent Cochrane reviews of randomized trials have assessed the association between ICS use and linear growth in children with persistent asthma. The first review with 25 trials shows that regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm/y in linear growth velocity and a 0.61-cm change from baseline in height during a one-year treatment period in children with mild to moderate persistent asthma [8]. ICS-induced growth suppression appears neither progressive nor regressive, and it is not cumulative beyond the first year of therapy. The second review with ten trials shows a small but statistically significant group difference in growth velocity over 12 months between low doses and low to medium doses of ICS, favouring the use of low-dose ICS, in prepubescent school-aged children with mild to moderate persistent asthma [9].

Randomized controlled trials are considered to be the best study design for assessing the efficacy of an intervention, however, evidence derived from randomized trials regarding ICS-related growth suppression in children with asthma may have limitations due to limited trial duration, fixed daily dose and high treatment adherence. Real-world observational studies may provide additional relevant information regarding the potential impact of ICS on the growth of children with asthma, but there are few such studies available [10-12].

This study aimed to assess the growth of children with persistent asthma taking regular ICS, compared to children with intermittent asthma who were not treated with ICS.

Methods

Methodological issues of the main research project

This article was based on the doctoral dissertation of Silveira DH. Parts of the results have been previously published [13]. Methodological issues of the main research project are briefly described below.

We conducted an observational study at the Pediatric Pulmonary Outpatient clinics of two university teaching hospitals in southern Brazil between April 2012 and May 2013. Children (3 - 12 yr) with diagnosis of asthma were eligible for the study. The diagnosis and classification of asthma [14,15] were performed by three senior pulmonologists who provided specialized care for asthmatic children at two study settings. Patients were seen regularly at an interval of one to three months, and their asthma control was assessed by three senior pulmonologists. Asthma control was classified as controlled, partly controlled and uncontrolled [14] and treatment regime was adjusted accordingly.

Children with persistent asthma taking regular ICS were classified as exposed group while those with intermittent asthma were classified as non-exposed group, recruited at a ratio of 2:1, matched by age groups: 3 - 6 years old and > 6 - 12 years old. Children with bronchopulmonary dysplasia, cystic fibrosis, congenital cardiopulmonary diseases, immunodeficiency and chronic encephalopathy were excluded from the study.

Child's parents or caretakers were interviewed by five well–trained investigators using a standardized pre–coded questionnaire. The questionnaire recorded demographic and socioeconomic data, birth data, child and parental health problems and use of medications. After the interview, we obtained child's anthropometric measures. The weight (kg) was measured by a mechanical platform scale with capacity up to 150 kg (Filizola®) and height (m) was measured by a stadiometer (Altura Exata) using standardized methodology [16].

Study variables and definition

The dependent variable was child's growth measured by height (cm), height-for-age [17] (stunting: <-2 Z-scores; normal: ≥ -2 Z-scores) and growth patterns. Growth patterns were classified into four categories: catch-up growth (stunted at birth, but normal height-for-age at time of study), suppressed growth (normal birth length, but stunted at time of study), persistent stunting (stunted at birth and at time of study) and normal growth (normal birth length and normal height-for-age at time of study).

The independent variables included age, gender, skin color, family income, parental school years, gestational age (preterm: < 37 weeks), birth weight (low birth weight: < 2.500g), birth length, maternal smoking during pregnancy, passive smoking, family history of asthma (first–degree relatives) and personal history of allergic rhinitis.

Statistical Analysis

Double data entry was performed using the software EPI-data 3.2. Analyses were carried out using Stata 11 (Stata Corp. College Station, USA). A descriptive analysis was conducted with calculation of absolute and relative frequencies for each variable. Pearson's chi-squared test or Fisher's exact test was used for comparing categorical data, and the Student's t-test was used for continuous data. We conducted subgroup analysis according to patient's age (3 - 6 yr vs. > 6 yr) given that clinical diagnosis of asthma may be less accurate in children under 6 years of age. Among children with persistent asthma taking regular ICS, we explored the potential influence of type of ICS, duration of use, asthma control and patient's age on child's growth through subgroup analyses. The p-value < 0.05 in two–tailed tests was defined as statistically significant.

Results

A total of 397 children with asthma were recruited in the main research; 323 patients who had anthropometric measures at birth and at time of study were included in this study. Of 323 included patients, 217 had persistent asthma taking regular ICS and 106 had intermittent asthma and did not use ICS. The characteristics of 323 patients are shown in table 1. Among 217 patients with persistent asthma, 162 used beclomethasone and 55 used other asthma controllers (fluticasone or budesonide, alone or associated with long-term beta-$_2$ agonists). Low to medium daily doses were used. The median duration of ICS use was 6 months, with an interquartile range (IQR) of 2 to 15 months. The data on asthma control was available in 307 patients, and asthma was controlled in 218 patients (71%), partly controlled in 63 patients (20.5%) and uncontrolled in 26 patients (8.5%).

Variables	Persistent asthma (n = 217)		Intermittent asthma (n = 106)		p value*
	n	%	n	%	
Gender					0.51
Female	92	42.4	49	46.2	
Male	125	57.6	57	53.8	
Skin color					0.53
White	143	66.2	74	69.8	
Non-white	73	33.8	32	30.2	
Gestational age					0.20
≥ 37 weeks	175	83.7	85	88.5	
< 37 weeks	34	16.3	11	11.5	
Birth weight					0.67
≥ 2.500g	191	88.0	89	86.4	
< 2.500g	26	12.0	14	13.6	
Birth length					0.78
≥ 2-Z scores	169	77.9	81	76.4	
< 2-Z scores	48	22.1	25	23.6	
Maternal smoking during pregnancy					0.06
No	167	77.0	91	85.9	
Yes	50	23.0	15	14.2	
Family income					0.97
1st tercile	76	37.1	37	35.9	
2nd tercile	57	27.8	30	29.1	
3rd tercile	72	35.1	36	34.9	
Maternal educational level					0.19
≥ 9 years	115	53.2	48	45.3	
< 9 years	101	46.8	58	54.7	
Paternal educational level					0.36
≥ 9 years	80	38.7	32	33.3	
< 9 years	127	61.3	64	66.7	
Passive smoking					0.63
No	127	58.5	68	64.2	
Yes	81	37.3	34	32.1	

Table 1: *Characteristics of study sample (n = 323).*

**p value for Pearson's chi-squared* test

The mean height (standard deviation) at time of study was 120.4 (16.3) cm in the persistent asthma group and 120.7 (16.7) cm in the intermittent asthma group (p = 0.89). Nine patients (2.8%) were stunted at time of study; five from the persistent asthma group and four from the intermittent asthma group (Table 2). Among 250 patients with normal birth length, 246 (98.4%) had normal height-for-age at time of study. Only four patients, two from each group, had suppressed growth pattern. Forty-eight (22.1%) patients from the persistent asthma group and 25 (23.6%) patients from the intermittent asthma group were stunted at birth. Most of these children in both groups (93.8% vs. 92.0%) had catch-up growth, achieving a normal height-for-age at time of study. No significant differences were observed between children with persistent asthma taking regular ICS and children with intermittent asthma in terms of stunting at time of study and growth pattern. The subgroup analysis by patient's age yielded the similar results (Table 2).

Asthma classification	Stunting at time of study		Catch-up growth		Persistent stunting		Suppressed growth		Normal growth	
	n/N (%)	p value*	n/N† (%)	p value*	n/N† (%)	p value*	n/N‡ (%)	p value*	n / N‡ (%)	p value*
All patients (n = 323)		0.48		1.00		1.0		0.59		0.59
Persistent asthma	5/217 (2.3)		45/48 (93.8)		3/48 (6.2)		2/169 (1.2)		167/169 (98.8)	
Intermittent asthma	4/106 (3.8)		23/25 (92.0)		2/25 (8.0)		2/81 (2.5)		79/81 (97.5)	
Patients aged 3-6yr (n = 145)		0.10		0.25		0.25		0.23		0.23
Persistent asthma	2/99 (2.0)		19/20 (95.0)		11/20 (5.0)		1/79 (1.3)		78/79 (98.7)	
Intermittent asthma	4/46 (8.7)		8/10 (80.0)		2/10 (20.0)		2/36 (5.6)		34/36 (94.4)	
Patients older than 6yr (n = 178)		0.55		0.54		0.54		1.00		1.00
Persistent asthma	3/118 (2.5)		26/28 (92.9)		2/28 (7.1)		1/90 (1.1)		89/90 (98.9)	
Intermittent asthma	0/60 (0)		15/15 (100.0)		0/15 (0)		0/45 (0)		45/45 (100.0)	

Table 2: *Comparison of growth between children with persistent asthma taking regular ICS and children with intermittent asthma (n = 323).*

**p value for Fischer's exact test; N†: Number of patients stunted at birth; N‡: Number of patients with normal birth length*

Table 3 shows growth patterns in children with persistent asthma according to ICS molecules, duration of use and patient's age. No significant differences in growth patterns were observed between beclomethasone and other ICS, between duration of ICS use ≤ one year and duration of use over a one-year period, between controlled asthma and partly controlled or uncontrolled asthma, and between patients aged 3 to 6 years and those older than 6 years of age.

ICS use	Catch-up growth		Suppressed growth		Persistent stunting		Normal growth	
	n/ N† (%)	p value*	n/ N‡ (%)	p value*	n/ N† (%)	p value*	n / N‡ (%)	p value*
Type of ICS		0.51		0.46		0.51		0.46
Beclomethasone	36/38 (94.7)		1/124 (0.8)		2/38 (5.3)		123/124 (99.2)	
Others	9/10 (90.0)		1/45 (2.2)		1/10 (10.0)		44/45 (97.8)	
Duration of use		1.00		0.10		1.00		0.10
≤ 1yr	25/27 (92.6)		0/102 (0)		2/27 (7.4)		102/102 (100.0)	
> 1yr	12/12 (100.0)		2/44 (4.5)		0/12 (0)		42/44 (95.5)	
Asthma control		1.00		1.00		1.00		1.00
Controlled	21/22 (95.6)		1/90 (1.1)		1/22 (4.5)		89/90 (98.9)	
Partly controlled or uncontrolled	23/25 (92.0)		1/64 (1.6)		2/25 (8.0)		63/64 (98.4)	
Patient's age		1.00		1.00		1.00		1.00
3-6 yr	19/20 (95.0)		1/79 (1.3)		1/20 (5.0)		78/79 (98.7)	
> 6yr	26/28 (92.8)		1/90 (1.1)		2/28 (7.1)		89/90 (98.9)	

Table 3: *Growth patterns in children with persistent asthma according to type of ICS, duration of use and patient's age (n = 217).*

**p value for Fischer's exact test; N†: Number of patients stunted at bir N‡: Number of patients with normal birth length*

Discussion

This hospital-based observational study shows no significant difference in mean height, stunting at time of study and growth pattern between children with persistent asthma taking regular ICS and those with intermittent asthma who were not treated with ICS. Among children with persistent asthma, ICS molecules, duration of use, asthma control and patient's age appear to have no significant impact on the effect size of ICS on child's growth pattern.

The prevalence of stunting at birth in both persistent and intermittent asthma groups (22.1% and 23.6%) was higher than that (12.4%) reported in a cohort of 4231 children born in 2004 from the same geographic region as this study [18]. However, most of patients who were stunted at birth in both asthma groups had catch-up growth, achieving a normal height-for-age at time of study. Overall, only 2.3% of children with persistent asthma taking regular ICS and 3.8% of children with intermittent asthma were stunted at time of study. The prevalence of stunting in both groups is similar to that (3.6%) reported in the above-mentioned birth cohort at four years of age. Only four patients (two from each group) had suppressed growth pattern, that is, they had normal birth length but were stunted at time of study. These results suggest that children with persistent asthma treated with regular ICS may have a normal growth, even if they were stunted at birth.

The subgroup analyses in patients with persistent asthma did not find significant differences in growth pattern between beclomethasone and other ICS, between short-term and long-term (> one year) use, between controlled asthma and partly controlled or uncontrolled asthma, and between preschoolers and older children. These findings provide some evidence that regular use of ICS may not significantly affect the growth of children, regardless of drug molecule, duration of use, asthma control and patient's age.

A limited number of observational studies have assessed the effects of asthma and treatment on child's growth. One large cohort study with 2355 children at primary care settings (69% of the population of the Tayside childhood asthma project) showed that neither asthma nor its treatment had noticeable effect on the height of most of the children [10]. Only a small subset of children who received high doses of ICS and used both general practice and hospital services had a significant reduction in their stature. Other two hospital-based studies also did not show a significant negative impact of ICS on the growth of children with asthma [11,12]. The difference across studies in design, patient populations and outcome measures does not allow direct comparison of observational studies.

Several limitations should be taken into account when interpreting the results of this study. Firstly, 18.6% of the participants from the main research were not included in the study due to unavailable anthropometric data, and this may raise concerns about the potential bias. However, there is no significant difference in terms of demographics (age, gender, ethnicity and family income) between included and non-included patients (data not shown), suggesting a comparable growth between the two groups. Secondly, asthma severity may have acted as a confounder given that both ICS and asthma severity could potentially negatively impact child's growth. However, as there is no significant difference in the growth between children with persistent asthma taking ICS and those with intermittent asthma not receiving ICS, the potential confounding effects of asthma severity may even strengthen the study's findings that regular use of ICS does not significantly affect the growth of children with persistent asthma. Thirdly, this is a real-world observational study in which the dose of ICS may have changed over time and the treatment adherence was not assessed. Fourthly, given that only 8.5% of patients had uncontrolled asthma, caution should be taken when extrapolating the findings of this study to children with uncontrolled asthma.

Conclusion

In conclusion, this observational study suggests that there is no significant difference in height and growth pattern between children with persistent asthma taking ICS and those with intermittent asthma who were not treated with ICS. These results add to the current evidence suggesting a good safety profile of ICS in children with persistent asthma.

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Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose.

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