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Effect of Inhaled Corticosteroids on Growth in Childhood Persistent Asthma

[1]Dr.Midhun Vasudevan, Junior Resident, Department of Pediatrics, Medical College Kozhikode

[2]Dr K.R Subharaman, Professor of Pediatrics, Department of Pediatrics, Medical College Kozhikode

[3]Dr Kasim Resivi Ullerithody, Associate Professor, Department of Pediatrics, Medical College Kozhikode

Corresponding Author: Dr Kasim Resivi Ullerithody, Associate Professor, Department of Pediatrics, Medical College Kozhikode

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Abstract

Introduction: Asthma is a common chronic inflammatory condition of airways resulting in episodic airflow obstruction both in children and adults.

The prevalence of asthma has increased dramatically, and asthma is now recognized as a major cause of morbidity, medical expense, and preventable death.

Advances in asthma management and especially pharmacotherapy have improved the prospect of all except a few children with asthma.

Medications for asthma are either controllers or relievers. Inhaled corticosteroids are the best controller medication currently available.

Inhaled corticosteroids have local and systemic side effects. One systemic side effect reported was it's impact on the growth of children.

In this setting, we planned to conduct a study to determine the effects of the inhaled steroids on growth in childhood persistent asthma.

Materials and methods

This was a Prospective cohort study conducted in Asthma clinic of Pediatric Department ,Institute of Maternal and Child Health medical College Kozhikode.

All children between the ages of 1 and 13 years attending the asthma clinic regularly were included.

They are classified into different cohorts based on the severity of asthma. Their length or height and weight was measured accurately.During subsequent visit at or after six months, weight and height are measured again and recorded.The difference in initial and final recording was calculated and weight velocity and height velocity were computed.

Discussion

The mean weight velocity was found to be decreased in all age groups who were on inhaled corticosteroids . An exception to this trend was found in girls of age groups more than 10 years with moderate persistent asthma who showed an increase in mean weight velocity.

A cumulative decrease in expected weight for the total duration 11 years [that is through 1 year to 12 years of age] in children on ICS.

Our study showed a decrease in mean weight velocity in children who were on ICS, comparable to other studies.

Different trends were observed in linear growth velocity in different age groups of children who were on inhaled corticosteroids therapy.

Conclusion

There was a decrease in mean weight velocity in children with persistent asthma on inhaled steroids, but it's significance was variable. The mean height velocity increases insignificantly in children of age group 4-12 years with the use of ICS . The mean height velocity significantly decreases as the duration of therapy with ICS is prolonged.

Keywords: Inhaled Corticosteroids; Growth; Children; Asthma.

Introduction

Asthma is a chronic inflammatory condition of airways resulting in episodic airflow obstruction. Different phenotypes with varying prognosis and and determinants have been described particularly in childhood years[1].

The prevalence of asthma has increased dramatically, and asthma is now recognized as a major cause of morbidity, medical expense, and preventable death.[2] Although the cause of childhood asthma has not been determined, research has implicated a combination of environmental exposures and inherent biologic and genetic vulnerabilities. Respiratory exposures in this causal environment include inhaled allergens, respiratory viral infections, and chemical and biologic pollutants such as tobacco smoke.

Once asthma has developed ongoing exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.in susceptible individuals, inflammation causes recurrent wheezing, breathlessness, chest tightness and coughing particularly at night or early in the morning. The inflammation also causes increase responsiveness to a variety of stimuli[3].

Asthma can be sub divided by severity based on the level of symptoms, airflow limitations, and lung function variability in to intermittent, mild persistent, moderate persistent and severe persistent asthma.

Asthma management is aimed at reducing the environmental exposures to stimuli, avoiding triggers, reducing inflammation by anti-inflammatory controller medications, and treating comorbid conditions that can worsen asthma. Advances in asthma management and especially pharmacotherapy, enables all but the uncommon child with severe asthma to live normally[4,5]

Although the cost of treatment of asthma seems high from the perspective of patient’s family and society, the cost of not treating is quite high.in asthma control refers to control of manifestations of the disease.

Medications for asthma are either controllers or relievers.it can be administered oral, parenteral, or inhaled. The major advantage of inhaled medications is that the drug delivered directly into the airways have quick onset of action producing least systemic side effects. Inhaled corticosteroids are the best controller medication currently available.

Inhaled corticosteroids have local and systemic side effects. Local effects include oral candidiasis, dysphonia and local irritation which can be minimized by gargling after use. Systemic effects are produced by when the drug is absorbed from lungs or and possibly stomach.t is dependent on the dose, potency, delivery system, bioavailability, half-life of the drug, and first metabolism. The side effects are decreased bone mineral density, easy bruising, and adrenal suppression. Many children receiving inhalational corticosteroids

experience a reduction in growth rate towards the end of first decade. This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of the puberty and delay in skeletal maturation. Adult height is not decreased although it is reached at a later age.[6]

In this setting, we planned to conduct a study to determine the effects the inhaled steroids on growth in childhood persistent asthma.

Materials and methods

Study design: Prospective cohort study

Study setting: Asthma clinic of Pediatric Department, Institute of Maternal and Child Health medical College Kozhikode.

Source of data: All children between the ages of 1 and 13 years attending the asthma clinic Conducted by department of Pediatrics for regular follow up are included in the Study. Detailed history and measurements done were recorded in a structured proforma.

Study period: 1st of October 2010 to31st of September 2011

Study subjects

Inclusion criteria: All children between the ages of 1- and 13-years attending asthma clinic regularly were Included.

Exclusion criteria

1. Children with growth retardation due to other systemic illness.
2. Children with moderate to severe malnutrition.
3. Children with short stature.
4. Children who received systemic steroids for more than once in any three months interval or more than 4 times in an year during the period of the study.
5. Children with severe persistent asthma.
6. Children who lost to follow up.

Sample size: A total of 257 cases were studied.

Methods

All children included in the study were evaluated with detailed and physical examination.

They are classified into different cohorts based on the severity of asthma as intermittent, mild persistent, moderate persistent. Their length or height was measured accurately to the nearest millimeter using an infantometer or stadiometer appropriately. Weight was measured in kilograms to the nearest single decimal using an electronic weighing machine with zero error of 10 grams.

In asthma clinic we use step down approach in which budesonide 400micrograms per day is started initially and based on clinical improvement assessed by a scoring system the dosage is tapered over 3- 6 months.

During subsequent visit at or after six months, weight and height are measured again and recorded, details about use of systemic steroids or other severe illness are enquired and recorded.

The difference in initial and final recording was calculated and weight velocity and height velocity were computed. The cohorts are then compared in different age groups and sex. Age groups were categorized based on the standard growth velocities at which normal children grow. Age groups categorized as age 1-2 years, 2-3 years,3-4 years,4-10 years, and above 10years for both boys and girls and data was analyzed.

Statistical analysis.

Data collected was analyzed using computer-based SPSS software.

Analysis was done using ANOVA and paired t-test.

Observation and results

Table 1: sex distribution

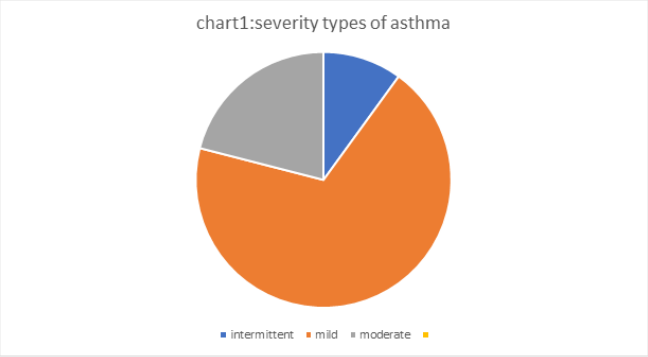
sex	Frequency	percent
Male	154	59.9
Female	103	40.1
total	257	

The male female ratio was1.5:1

Out of 257 cases studied, types of asthma according to severity as the table 2 and chart2 below:

Table 2: severity types of asthma

Severity type	frequency	Percent
Intermittent	27	10.5
Mild	176	68.5
Moderate	54	21
total	257	100



Age distribution of children studied were as in the table 3 and chart 3 as given above.

Table 3: Distribution of cases according to age groups

Age group	Frequency	Percent
1 -2	22	8.6%
2 -3	35	13.6%
3 -4	33	12.8%
4 - 10	126	49.0%
>10	41	16.0%
Total	257	100.0%

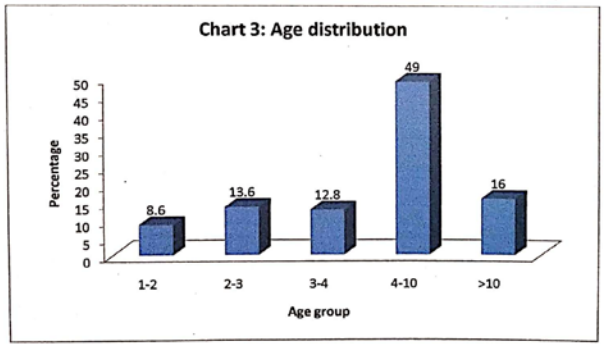


Table 4: Distribution of cases in different age groups based on the severity types of asthma

Age group (years)	Severity types of asthma			Total
	Intermittent	Mild	Moderate	
1 -2	3	14	5	22
	13.6%	63.6%	22.7%	100.0%
2 -3	5	26	4	35
	14.3%	74.3%	11.4%	100.0%
3 -4	4	26	3	33
	12.1%	78.8%	9.1%	100.0%
4 - 10	13	84	29	126
	10.3%	66.7%	23.0%	100.0%
>10	2	26	13	41
	4.9%	63.4%	31.7%	100.0%
Total	27	176	54	257
	10.5%	68.5%	21.0%	100.0%

Table 5: Distribution of mean weight and height velocity in different severity types of asthma in boys of age group 1 -2 years

Type		Weight velocity	Height velocity
Intermittent	Cases	1	1
	Mean	3.003	10.626
	SD	3.003	10.626
Mild	Cases	10	10
	Mean	1.755	8.874
	SD	.707	2.175
Moderate	Cases	5	5
	Mean	2.264	10.609
	SD	1.279	2.587

P value> 0.05

Children with mild persistent asthma who were on inhaled corticosteroids (ICS)had a decrease in mean weight velocity of 1.248 kg/yr, and moderate persistent asthma had a decrease in 0.739kg/yr. decrease when compared to children with intermittent asthma who were not on ICS.The decrease in mean height was not significant as in table 5.

There was a decrease in mean height velocity of 1.752cm/yr in mild persistent asthma and 0.017cm/yr. in moderate persistent asthma when compared to intermittent asthma. The decrease was not significant statistically.

Table 6: Distribution of mean weight and height velocity in different severity types of asthma in girls of age group 1 -2 years

Type		Weight velocity	Height velocity
Intermittent	Cases	2	2
	Mean	2.545	10.118
	SD	1.141	2.019
Mild	Cases	4	4
	Mean	2.275	10.928
	SD	1.763	3.013

P value > 0.05

In girls in the age group 1-2 years, with mild persistent asthma on ICS had decrease in mean weight velocity of 0.27kg/year when compared to children with intermittent asthma.it was not statistically significant.

There was an increase in men height velocity of 0.81cm/year in mild persistent asthma when compared to intermittent asthma. This increase also was not significant as in table 6.

In case of boys in the age group of 2-3 years, those with mild persistent asthma on ICS had a decrease in mean weight velocity of 0.81kg/year, and moderate persistent asthma had decrease in 0.912kg/year decrease when compared with intermittent asthma. The decrease in weight velocity ws not significant. There was decrease in mean height velocity of 0.359cm/year in mild persistent asthma and 0.865cm/year in moderate persistent asthma when compared to intermittent asthma. These decreases were not statistically significant as in table 7 and chart 5.

Among girls of age 2-3 years, those with mild persistent asthma on ICS had an increase in mean weight velocity of 0.425kg/yr. and moderate asthma had a decrease in of 0.014kg/yr. when compared to those with intermittent asthma. The difference was not significant. There was a decrease in mean height velocity of 0.696cm/year in mild persistent asthma and1.505cm/year in moderate persistent asthma when compared to intermittent asthma. These decreases were not significant statistically as in table 8 and chart 5.

Boys with mild persistent asthma in the age group 3-4 years who were on ICS had a decrease in in weight velocity of 1.599kg/yr., and moderate persistent asthma had a decrease in 1.852kg/yr decrease when compared to children with intermittent asthma not on ICS.This decrease was not significant. There was a decrease in mean height velocity f 0.097cm/year in mild persistent asthma and 0.295cm/year increase in moderate persistent asthma when compared to intermittent asthma. These differences were not significant statistically as in table 9 and chart 6.

Among girls of 3-4 years, those with mild persistent asthma on ICS had a decrease of2.316kg/year in mean

weight velocity when compared to intermittent asthma. The decrease was statistically significant. There was aa decrease in mean height velocity of 1.454cm/yr in mild persistent asthma when compared to intermittent asthma. This decrease was not significant as shown in table10 and chart6.

Table 8: Distribution of mean weight and height velocity in different severity types of asthma in girls of age group 2-3 years

Type		Weight velocity	Height velocity
Intermittent	Cases	1	1
	Mean	1.293	8.335
Mild	Cases	11	11
	Mean	1.718	7.639
	SD	0.443	1.696
Moderate	Cases	3	3
	Mean	1.279	6.83
	SD	1.694	3.815

p value>0.05

Chart 5: Growth velocity in boys and girls of age group 2-3

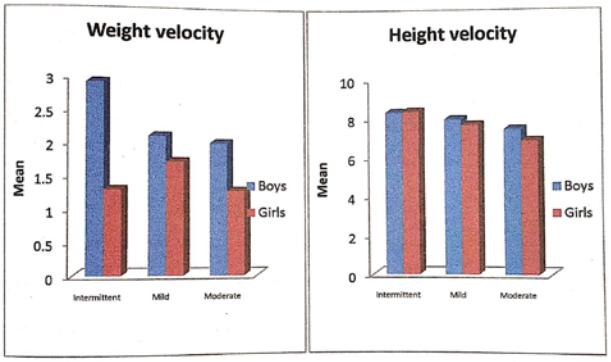


Table 9: Distribution of mean weight and height velocity in different severity types of asthma in boys of age group 3-4 years

Type		Weight velocity	Height velocity
Intermittent	Cases	3	3
	Mean	3.599	8.037
	SD	1.026	1.711
Mild	Cases	13	13
	Mean	1.96	7.94
	SD	1.07	1.712
Moderate	Cases	3	3
	Mean	1.707	8.332
	SD	0.455	0.883

P value > 0.05

Chart 6: Growth velocity in boys and girls of age group 3-4

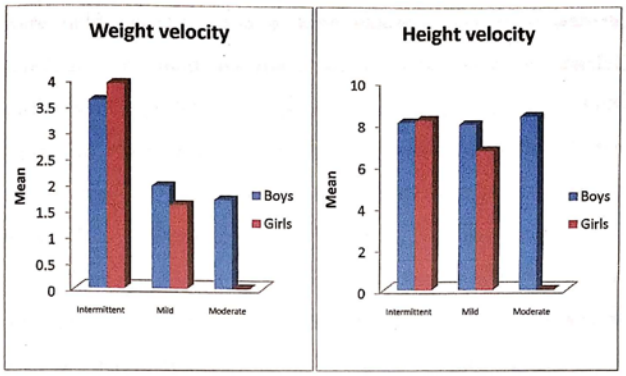


Table 11: Distribution of mean weight and height velocity in different severity types of asthma in boys of age group 4-10 years

Type		Weight velocity	Height velocity
Intermittent	Cases	10	10
	Mean	2.281	5.427
	SD	1.399	2.7
Mild	Cases	48	48
	Mean	2.102	6.099
	SD	1.406	1.823
Moderate	Cases	17	17
	Mean	2.373	6.369
	SD	1.56	1.554

P value > 0.05

Table 12: Distribution of mean weight and height velocity in different severity types of asthma in girls of age group 4-10 years

Type		Weight velocity	Height velocity
Intermittent	Cases	3	3
	Mean	2.963	4.903
	SD	1.423	0.055
Mild	Cases	36	36
	Mean	2.631	5.95
	SD	2.003	1.509
Moderate	Cases	12	12
	Mean	1.796	5.629
	SD	1.146	1.817

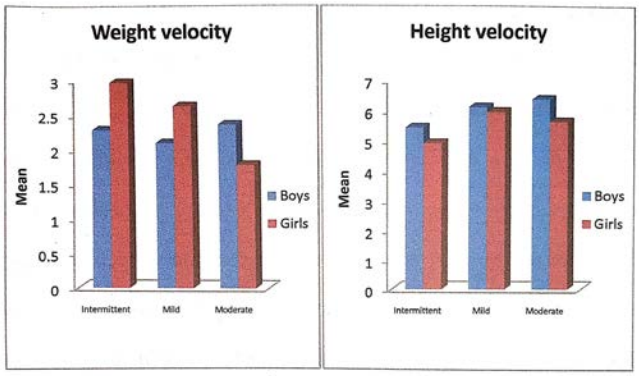
P value > 0.05

As shown in the table 11 and chart 7, among boys in the age group o 4-10 years with mild persistent asthma on ICS had a decrease in mean weight velocity of 0.179kg/yr. and moderate persistent asthma had an increase in 0.092kg/yr. when compared to intermittent asthma not on ICS. These differences were not significant. There was an increase in mean height

velocity of 0.672cm/year in mild persistent asthma and 0.942cm/year in moderate persistent asthma when compared to those with not on ICS.These differences was not significant statistically.

Among girls in the age group 4-10 years, those with mild persistent asthma on ICS had a decrease in mean weight velocity of 0.332kg/year and moderate persistent asthma had a decrease in 1.167kg/year when compared to intermittent asthma. This decrease was not significant. There was an increase in mean height velocity of 1.047cm/year in mild persistent asthma and 0.726cm/year in moderate persistent asthma when compared to intermittent asthma. This increase was not significant. Asin table12 and chart7.

Chart 7: Growth velocity in boys and girls of age group 4-10



Boys who are I above 10 years with mild persistent asthma on ICS had a decrease in mean weight velocity of 0.686kg/year and moderate persistent asthma had a decrease in 0.086kg/year decrease when compared to children with intermittent asthma not on ICS.The decrease was not significant. There was an increase in mean height velocity of 1.538cm/year in mild persistent asthma and 1.402cm/year in moderate persistent asthma when compared to intermittent asthma which are detailed in table13 and chart 8.

Among girls above 10 years, who had mild persistent asthma on ICS had a decrease in weight of 1.225kg/year when compared to moderate persistent asthma not on ICS.The difference was not significant. There was decrease in mean height velocity of 2.848cm/year in moderate persistent asthma when compared to mild persistent asthma. This decrease was statistically significant as depicted in table 14 and chart 8.

Of 225 children who were on inhaled orticostroids,158 were new cases whose duration of treatment is less than 1 year and 67 were on ICS for more one year. The mean weight velocity was decreased in old cases compared to new cases. This difference was not statistically significant. The men height velocity was decreased in old cases by0.66cmm/year compared to new cases. The decrease was statistically significant as depicted in table 15 and chart 9.

Table 13: Distribution of mean weight and height velocity in different severity types of asthma in boys >10 years

Type		Weight velocity	Height velocity
Intermittent	Cases	2	2
	Mean	3.138	4.225
	SD	4.947	1.399
Mild	Cases	14	14
	Mean	2.452	5.763
	SD	3.074	1.404
Moderate	Cases	8	8
	Mean	3.052	5.627
	SD	1.416	1.423

P value > 0.05

Table 14. Distribution of mean weight and height velocity in different severity types of asthma in girls > 10 years

Type		Weight velocity	Height velocity
Mild	Cases	12	12
	Mean	3.238	6.489
	SD	2.184	1.423
Moderate	Cases	5	5
	Mean	4.463	3.641
	SD	2.44	3.186
p value			<0.05

F value 8.528

Chart 8: Growth velocity in boys and girls of age group >10

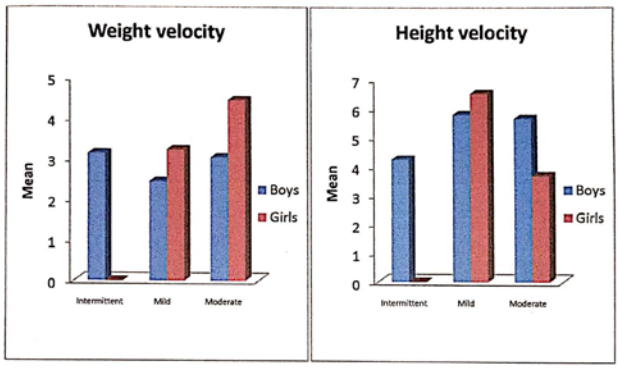
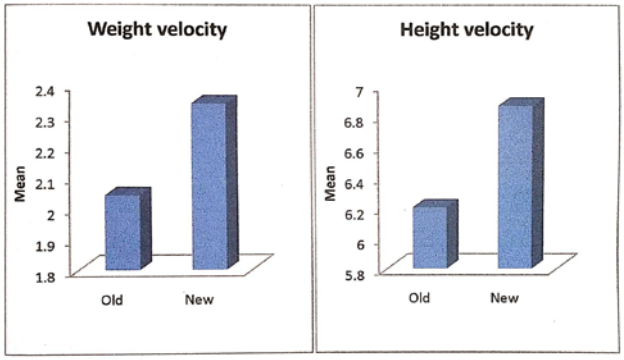


Table 15: Comparison of growth velocity in children based on the duration of treatment with inhaled corticosteroids

	Duration	N	Mean	Std. Deviation	Std. Error Mean
Wt velocity	Old	67	2.042	1.438	0.175
	New	158	2.340	1.731	0.137
Ht velocity	Old	67	6.203	1.680	0.205
	New	158	6.863	2.401	0.191

P value <0.05; F = 4.533

Chart 9: Growth velocity in children based on duration of treatment



Discussion

A total of 257 cases were included in our study. Out of these,154 were males and 103 were females. the male to female ratio was approximately 3:2 which was comparable with other studies. This is because the lung volume is less in males during birth than females but as age advances towards adulthood , the sex ratio becomes equal or prevalence among females increases slightly [7] .We divided the children in to 1-2 years 2-3 years and 3-4 years and 4-10 years and more than ten years . All children included in the study were under the age 12 years. mean weight velocity and mean height velocity were calculated.

Mean weight velocity

The mean weight velocity was found to be decreased in all age groups who were on inhaled corticosteroids [mild and moderate persistent asthma] as compared to those who were not on ICS [intermittent asthma] . An exception to this trend was found in girls of age groups more than 10 years with moderate persistent asthma who showed an increase in mean weight velocity as compared to those who were not on ICS. Still they did not attain mean weight velocity according to Indian standards as per Agarwal et al[8,9] . This was probably due to changes in secular trends [10,11] in Indian childhood population over past 18 years.

	Standards for India (Agarwal et al)		Intermittent asthma		Mild persistent asthma		Moderate persistent asthma	
Age(yrs)	boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1-2	2.6	2.6	3	2.55	1.75	2.26	2.26	-
2-3	1.9	1.9	2.9	1.29	2.1	1.72	2	1.28
3-4	1.6	1.6	3.6	3.92	1.96	1.6	1.71	-
4-10	2.5	2.5	2.28	2.96	2.10	2.63	2.37	1.8
More than 10	3.35	4.55	3.14		2.45	3.24	3.05	4.46

Accumulative decrease in expected weight for the total duration 11 years [that is through 1 year to 12 years of age] in children on ICS, as compared to those who were not on ICS was obtained in this study.

For boys with mild persistent asthma there was a cumulative decrease of 6.01 kg in expected weight and for those who with moderate persistent asthma, a total decrease of 3.17 kg was obtained. For girls, the cumulative decrease in expected weight for this duration was 6.79 kg and 7.14 kg for mild persistent asthma and moderate persistent asthma, respectively.

Our study showed a decrease in mean weight velocity in children who were on ICS, which was comparable with studies by Cohen et al[12], Mc Nicol and William et al[13] and Snyder et al[14] . however, studies by Van Metre et al[15] showed no decrease or increase in mean weight velocity.

Mean height velocity

In our study different trends were observed in linear growth velocity in different age groups of children who were on inhaled corticosteroids therapy [mild and moderate persistent asthma].

	Standards for India (Agarwal et al)		Intermittent asthma		Mild persistent asthma		Moderate persistent asthma	
Age(yrs)	boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1-2	11.7	11.5	10.62	10.12	8.87	10.93	10.61	-
2-3	8.4	8.3	8.29	8.34	7.93	7.64	7.42	6.83
3-4	6.4	6.5	8.40	8.14	7.94	6.69	8.33	-
4-10	5.47	5.9	5.43	4.90	6.90	5.95	6.37	5.63
More than 10	6.1	5.4	4.23	5.4	5.76	6.49	5.63	3.64

Mean height velocity [cm/year]

In children of either sex in age group of 1-4 years who were on ICS

[mild and moderate persistent asthma] showed a decrease in mean height velocity as compared to children who were not on ICS [intermittent asthma]

This result of our study was comparable to Cochrane meta-analysis by Paul J Sharek et al[16] .

Cumulative decrease in expected height for these 3 years of duration [that is through 1-4 years of age] I was obtained as below.

For boys, this total reduction in expected height was 2.57 cm and 1cm respectively for mild and moderate persistent asthma.

For girls, this decrease in expected height was 1.35 cm and 2.55 cm respectively for mild and moderate asthma.

In age group of 4-12 years it was observed that the mean height velocity was higher that children who were on ICS as compared to those who are not on ICS. an exception to this trend was found in girls of 10-12 years were moderated persistent asthma whose mean height velocity was decreased. it was probably due to inadequate sample size.

Cumulative gain in expected height for this 6-year-old duration [through 4-10 years of age] was obtained as follows.

For boys, total increase in expected height was a 4.02 cm and 5.64 cm for mild and moderate persistent asthma, respectively.

For girls, total gain in expected height for these 6 years were 6.3cm and 4.36 cm respectively for mild and moderate persistent asthma.in the same age group it was observed that the linear growth velocity tended to decrease as the severity of asthma increased. The cumulative gain in expected height for 2 years duration (10-12 years) was obtained as given. Boys in this age group showed a total gain in expected height 3.06 cm for mild persistent asthma and 2.8cm for moderate persistent asthma.

Girls with moderate persistent asthma showed a total decrease of 3.52cm for these two years which was probably due to small sample size, whereas girls with mild persistent asthma showed a gain of 2.18 cm in expected height.

These increases in linear growth velocity was in contrast to several studies like Dawson et al[17] Paul J Sharek et al,[16]Chan…g et al[18]Synder et al[14] Cohen et al etc. which showed a decrease in linear growth velocity in children on ICS. However, there were several studies showing which showed no decrease in mean height velocity like Van Metre et al[16] and Spock et al[19].

Study by Falliers et al[20] an insignificant increase in mean height velocity which is like the results of our study.

In developing countries like India, asthma is still underdiagnosed and the uncontrolled disease itself retards the growth. Once the child has been started on ICS, there was prompt control resulting in catch – up growth in these children. This may be the reason for increase in linear growth velocity shown by children who were started on ICS in our study group.

Duration of Inhaled Corticosteroids And Growth

Of 225 children I age group 1-12 years studied, 158 were new cases with duration of ICS less than one year and 67 were on ICS for more than 1 year.

On comparing the mean weight velocity of these two groups, a decrease in mean weight velocity of 0.3 kg/yr. was found in children who were on ICS for more than 1 year. a cumulative reduction of 3kg in expected weight was found in these children. This decrease in weight gain might be because of long-term ICS.

when mean weight velocity between two groups was compared, it was found that the children who were on ICS for more than one year duration showed a decrease of 0.66cm /yr. in linear growth velocity. This may imply the linear growth retarding effect on long term inhaled corticosteroids.

Conclusions

There was a decrease in mean weight velocity in children with persistent asthma on inhaled steroids, but it was not statistically significant when treatment is less than one year. When the duration of therapy is prolonged this decrease become significant. The mean height velocity increases insignificantly in children of age group 4-12 years with the use of ICS by the optimization of growth potential due to prompt control of asthma resulting in catch up growth.

The mean height velocity significantly decreases as the duration of therapy with ICS is prolonged. Uncontrolled childhood persistent asthma can cause growth retardation.

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