EFFECTS OF LONG-TERM TREATMENT WITH AN INHALED CORTICOSTEROID ON PHYSICAL DEVELOPMENT AND PULMONARY FUNCTION IN ASTHMATIC CHILDREN

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ABSTRACT

Background: *Chronic airway inflammation is a common characteristic of the diverse illness known as asthma. During the last two decades, the prevalence of childhood asthma has significantly grown. More people are using inhaled corticosteroids to treat pediatric asthma as a maintenance measure.*

Aim of the study: *To assess the long-term impacts of inhaled corticosteroids on the physical development and pulmonary functions of asthmatic children.*

Subjects and methods: *This study had been done at Pediatric Allergy& immunology unit at Sayed Galal University Hospital in the period from November 2021 till October -2022. Our study was carried out on 120 patients who were diagnosed with bronchial asthma according to GINA-2022 and they divided into two groups:*

1. ***Group 1:*** *includes 80 patients with mild and moderate bronchial asthma receiving low dose (200 mcg /day beclometasone inhaled ICS*
2. ***Group 2:*** *included 40 patients with severe bronchial asthma receiving high dose (400mcg/day) beclometasone inhaled ICS.*

Results: *There was a statistically Significant differences between the two groups regarding to Respiratory score, FEV1 /FVC. Regarding physical development, there was no statistical Significant differences between the two groups.*

Conclusion: *the present study showed that the long-term use of ICS has no significant effect on physical development of asthma patients & the use of high dose ICS was linked with better improvement in pulmonary functions compared to low dose.*

Key words: *Corticosteroid, physical development, pulmonary function, asthmatic children.*

INTRODUCTION

Chronic airway inflammation is a common characteristic of the diverse illness known as asthma. It is identified by a history of respiratory symptoms, including wheezing, chest tightness, cough, and shortness of breath, together with a restriction of the expiratory airflow. The prevalence of asthma varies depending on the age of the population being studied and the diagnostic standards being used. It seems that the worldwide asthma incidence varies from 1% to 18% of the population in various nations, based on the use of standardized methodologies to evaluate the incidence of asthma and wheezing sickness in children and adults. **(Reddel et al., 2022)**. Throughout the last two decades, there has been a significant improvement in our understanding of the overall burden of childhood asthma. The International Study of Asthma and Allergies in Children (ISAAC), which included 306 sites in 105 countries, is primarily responsible for this improved knowledge. **(Soriano et al., 2017)**. Asthma is characterized by airway hyper responsiveness, which manifests as a disproportionate bronchoconstrictor response to a number of stimuli. **(Chapman et al., 2015)**. Children with asthma under controlled conditions in a clinical setting. Under these conditions there was no indication that long term treatment with inhaled budesonide adversely affected growth. ICS Inhaled corticosteroids are recommended as first line anti inflammatory therapy for the treatment of asthma. Many short and long term studies have shown ICS to be of benefit in children with asthma. However concern about the potential for systemic adverse events, including linear growth and bone metabolism, has resulted in reluctance on the part of many physicians and parents to use ICS. In this study we evaluated the long term effects of inhaled budesonide and found that long term ICS treatment did not cause any serious side effects in children growth and development **All-ergol et Immunopathol (2015)**. The reports on the effect of ICS have been controversial retarded growth and completely normal growth have been reported. It was concluded that there is no significant evidence of adverse effects on growth when conventional doses (< 400 _g/day) of ICS used. Growth retardation was not detected in any patients for the real effect of ICS on growth of asthmatic children, good information for their growth before the treatment with ICS should be available **Allergy et al; (2019)**.

AIM OF THE STUDY

In this study, we aimed to assess the long-term impacts of inhaled corticosteroid on the physical development and pulmonary functions of asthmatic children.

PATIENTS AND METHODS

A. Ethical consideration:

1. An informed consent was obtained from parents or legal guardians before getting involved in the study.
2. The study was done after approval of ethical committees of pediatrics department & faculty of medicine for Al-Azhar University.
3. The authors declared no potential conflicts of interest with respect to research, authorship, and\or publication of this article.
4. All the data of patients & results of the study are confidential & the patients have the right to keep it.
5. The parents have the right to withdraw from the study at any time without giving any reasons.

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B. Sample size calculation:

*According to Epi. Info 2000; the sample size was computed with a precision of (2%); a 95% confidence interval; and a sample size of 120 children with asthma exacerbation. In order to address issues with non-responses and missing data; the sample size was expanded by 10%.

85% of the study's power was used in the analysis.

*A sample type: (CDC Epi infoV7.0.8.3.

C. Inclusion Criteria:

1. Age: From 5 – 18 years old.
2. Sex: both male and female.
3. Patients diagnosed as bronchial asthma by pediatric pulmonologist.

D. Exclusion criteria:

1. Children < 5 years or >18 years.
2. Any lung condition other than bronchial asthma, for instance (bronchiectasis, cystic fibrosis).
3. un cooperated children including patients has intellectual or physical dis ability.
4. Short stature children.

5. Refusal to take part in the research.

E. Study design:

This is analytical follow- up study that was carried out during the period from November 2021 to October 2022 on 120 asthmatic patients either mild, moderate, severe according to GINA 2022.

They were selected by simple random method from Pediatric Allergy& immunology unit at Sayed Galal University Hospital.

Study method:

All the studied patient were classified into 2 groups:

1. **Group 1:** had patients with mild and moderate bronchial asthma receiving low dose (100-200 mcg /day) beclometasone inhaled ICS (include 80 patients).
2. **Group 2:** included patients with severe bronchial asthma receiving high dose (300-400mcg/day) beclometasone inhaled ICS (include 40 patients).

All patients were subjected to the following:

1. Careful history taking based on: Age, sex, symptoms of asthma, degree of asthma, family history of atopy, physical develpement of asthmatic children.
   - Family history:
   - Previous sibling with asthma.
2. Thorough clinical examination including:

- General examination: include color, heart rate, respiratory rate and temperature.
- Anthropometry and Z scores according to the new growth charts (include Weight, Length and Body mass index).

Follow up of anthropometric measurement after regular intake of ICS for asthma control after 12 months.

3. Investigations:

Complete Blood Count and absolute eosinophilic count (total leucocytes count x eosinophilic percentage).

Pulmonary function test:

All patients performed full spirometric evaluation using (Blue cherry-Spiro+F/V) which include maximal voluntary ventilation MVV, forced vital capacity FVC, and vital capacity VC and pulse oximetry).

Technique:

The patient must place the mouthpiece in their mouth, and the technician must ensure that there are no leaks, and the patient is not obstructing the mouthpiece. The

procedure is carried out as follows:

1. The patient must breathe in as much air as they can with a pause lasting for less than 1s at the total lung capacity.
2. The mouthpiece is placed just inside the mouth between the teeth, soon after the deep inhalation. The lips should be sealed tightly around the mouthpiece to prevent air leakage.

   Exhalation should last at least 6 seconds, or as long as advised by the instructor. If only the forced expiratory volume is to be measured, the patient must insert the mouthpiece after performing step 1 and must not breathe from the tube.
3. If any of the maneuvers are incorrectly performed, the technician must stop the patient in order to avoid fatigue and re-explain the procedure to the patient.
4. The procedure is repeated in intervals separated by 1 minute until two matching, and acceptable results are acquired **(Lamb et al., 2020)**.

Statistical analysis:

- Statistical analysis was done by SPSS version 28 (IBM Co., Armonk, NY, USA).
- Unpaired T test was used to assess quantitative parametric data, which were provided as mean and standard deviation (SD).
- Paired Student t-test was utilized to compare the means of two measurements belonging to the same subject.
- Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate.
- The overall diagnostic performance of each test was assessed by ROC curve analysis. The area under the curve (AUC) evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance for the test).
- Statistical significance was defined as a two-tailed P value <0.05.

RESULTS

The results of our study Will be summarized in the following tables & figures:

Table (1): Demographics of the studied groups

		Group I (n=80)	Group II (n=40)	P value
Age (year)		8.83 ± 3.01	8.13 ± 2.68	0.215
Sex	**Male**	46 (57.5%)	24 (60%)	0.947
	Female	34 (42.5%)	16 (40%)	

This table showed that there is no statistically significant difference between both groups regarding age or sex.

Table (2): BMI (kg/m2) of the studied group

		Group I (n=80)	Group II (n=40)	P between groups
BMI (kg/m^2)	**Baseline**	19.21 ± 4.39	18.8 ± 3.76	0.621
	After1 year	19.99 ± 4.83	19.58 ± 3.71	0.638
P between baseline &follow up		0.285	0.356	---

This table showed that BMI changes from baseline & the one-year assessment were not substantially distinct between groups I and II.

Table (3): Z-score of the studied group

		Group I (n=80)	Group II (n=40)	P value
Z-score	**Baseline**	0.028 ± 1.05	-0.068 ± 0.9	0.621
	After1 year	0.027 ± 1.08	-0.065 ± 0.83	0.638
P between baseline &follow up		0.992	0.987	---

This table showed that Z score after 1 year evaluation was not substantially distinct as compared to baseline in group I and group II.

Table (4): FEV1 /FVC ratio (%) test of the studied groups

		Group I (n=80)	Group II (n=40)	P value
FEV_1 /FVC ratio	**Baseline**	75.23 ± 7.14	72.1 ± 4.35	**0.012***
	After 1 year	79.01 ± 6.33	74.98 ± 5.07	**0.001***
P- value between baseline & follow up		**0.001***	**0.008***	**---**

FEV: Forced expiratory volume, FVC: Forced vital capacity.

This table showed that after 1 year follow up, FEV1 /FVC ratio was increased as compared to baseline in group I and group II. (P value <0.001).

Change in FEV1 /FVC ratio was substantially lower in group II than group I.

Table (5): Diagnostic performance of FEV1/FVC ratio in predicting severe bronchial asthma before and after ICS

		Cut off point	Sensitivity	Specificity	PPV	NPV	AUC	P value
FEV_1/ FVC ratio	**Baseline**	≤75	95%	52.5%	50	95.5	0.634	**0.008***
	1 year	≤80	95%	36.25%	42.7	93.5	0.659	**0.001***

This table showed that FEV1/FVC ratio is also a significant predictor of severe bronchial asthma incidence with AUC of 0.634 and p value =0.008. At cut off point ≤75, it with sensitivity of 95%, specificity of 52.5%, PPV of 42.7and NPV of 95.5.

1 year post ICS, FEV1/FVC ratio has a good diagnostic ability of predicting severe bronchial asthma incidence with AUC of 0.659 and p value=0.001. At cut off ≤80, it has sensitivity of 95%, specificity of 36.25, PPV of 42.7 and NPV of 93.5.

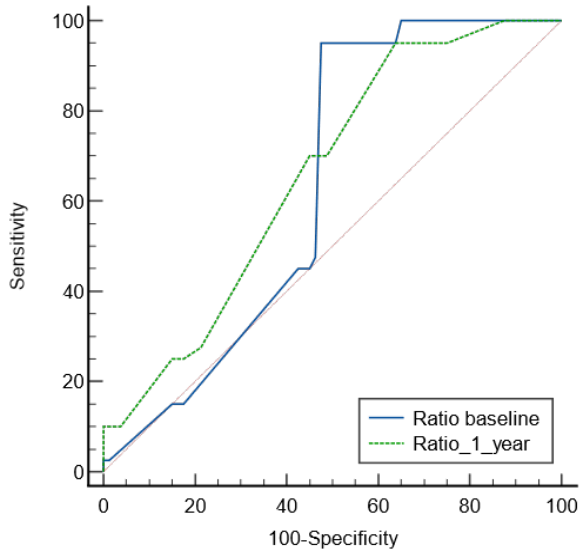

Figure (2): ROC curve of FEV1/FVC in predicting severe bronchial asthma before and after ICS

DISCUSSION

Asthma, a condition marked by reversible airflow restriction, inflammatory changes in the airways, and hyper reactivity of the airways, was shown to impact more than 272 million people globally in 2020. Children were especially susceptible (~ 7.0%). **(James et al., 2021)**. With the enormous number of kids who have asthma, there have been ongoing discussions and worries about asthma's possible effects on development **(Zhang et al., 2019)**.

The current study enrolled two matched groups regarding age and sex. There was no significant difference between mild/moderate (low dose ICS) and severe (high dose ICS) groups as regard baseline weight and the weight after 1 year of treatment.

As regard BMI, it was increased substantially in both groups, but there was no significant difference between the studied groups as regard the BMI at baseline and 1-year of treatment as well as the change in BMI was similar in both groups.

Also, z-score was increased substantially in both groups, but there was no significant difference between the studied groups as regard the z-score at baseline and 1-year of treatment as well as the

change in z-score was similar in both groups.

This was supported by, **Ortemenka, 2022** who aimed to assess the physical growth of 50 children who have received ICS at low, medium, or high doses as background long-term controller medication for their asthma. The research found no statistically substantial impact of extended background treatment with low/medium or high-dose ICS on the physical growth of asthmatic students.

Also, the current study was supported by a case-control study of **Sarıca et al., 2021** who concluded that Body composition measurements in asthmatic youngsters who use inhaled steroids don't appear to be impacted. Nevertheless, as the length of inhaled corticosteroid therapy grew, so did the percentage of body fat, the mass of body fat, and the hip circumference.

Moreover, **Li et al., 2015** who studied 112 children's bronchial asthma management effectiveness and the impacts of corticosteroid inhalation on growth and development were examined. Results revealed that ICS therapy for a year had no discernible impact on the children 's growth and advancement.

Also, **Kunøe, 2021** concluded that Early exposure to ICS was linked to a higher BMI z-score at age 6, an earlier adiposity rebound, and a rising trend of connection with a higher body fat percentage in children. The disparity may result from the different sample sizes and research contexts.

In our study the respiratory rate was substantially varied between the study groups, this difference was clinically non-significant as both groups were in normal range of respiratory rate.

Our results were agreed with **Arnold et al., 2016** who revealed that in children with asthma, respiratory rate is correlated with pulmonary function and clinical severity.

Regarding pulmonary functions among the studied groups, it was revealed that Forced expiratory volume (FEV1) was substantially greater in severe group (high dose) compared to mild/moderate group (low dose).

Forced expiratory volume/ forced vital capacity (FEV1/ FVC) ratio, after 1 year follow up, it was increased as compared to baseline in severe group (high dose). (P value <0.001).

Change in FEV1 /FVC ratio was substantially reduce in

mild/moderate group (low dose) than severe group (high dose).

Our results showed that higher dose of ICS was associated with better improvement in pulmonary functions.

In line with the study **Yamada et al., 2022** showed that Inhaled corticosteroid (ICS) usage between the ages of 10 and 12Y and high-dose ICS use between the ages of 13 and 15 Y were linked to improved lung function changes in children with asthma. The potential link between annual variations in lung function and inadequate asthma management and ICS dosage has to be taken into consideration.

Our findings were corroborated by **Li et al., 2015** who revealed that long-term regular inhalation corticosteroids perform good in controlling clinical symptoms and improving pulmonary functions compared with intermittent inhalation in children with asthma.

ROC curve analysis was performed and showed that before FEV1/FVC ratio is also a significant predictor of severe bronchial asthma incidence with AUC of 0.992 and p- value<0.001. At cut off point ≤80%, with sensitivity of 97.5%, specificity of 83.75%, PPV of 75 and NPV of 98.5.

At 1 year post ICS, FEV1/FVC ratio has a good diagnostic ability of predicting severe bronchial asthma incidence with AUC of 0.939 and p value<0.001. At cut off point ≤80%, with sensitivity of 97.5%, specificity of 83.75%, PPV of 75 and NPV of 98.5.

The current study showed that both FEV1 and FEV1/FVC have similar diagnostic accuracy to predict severe bronchial asthma before ICS treatment, but 1 year after treatment only FEV1/FVC still a reliable predictor of severe bronchial asthma.

Our findings were corroborated by **Francisco et al., 2015** who evaluated several spirometry airflow obstruction measurements in children with asthma and revealed that FEV1/FVC was more sensitive than FEV1 in predicting severe bronchial asthma in children.

However, in contrast to our results **Ratageri et al., 2001** revealed that FEV1 and FVC are inferior markers for determining the severity of asthma than FEF25% and FEF75%. The FEV1/FVC ratio is useless.

Also, **Lambert et al., 2015** showed that with various pre-test probability, the most precise FEV1/FVC threshold to diagnose asthma differed significantly. Consequently, it is crucial to take

the pre-test likelihood into account when interpreting spirometry for the diagnosis of asthma based on airflow restriction.

Moreover, **Meneghini et al., 2017** showed that Asthma spirometry abnormalities had a 90% specificity, 23% sensitivity, 22% PPV, and 91% NPV.

CONCLUSIONS

In conclusion; the current study showed that the long-term use of ICS has no clear effect on physical development of asthma patients. The usage of high dose ICS was linked with better improvement in pulmonary functions compared to low dose.

RECOMMENDATION

As the first line of anti-inflammatory medication for the treatment of asthma, inhaled corticosteroids are advised. Many trials, both short-term and long-term, have shown the value of ICS for asthmatic kids.

Our findings need to be confirmed by more comparative studies with bigger sample sizes and longer follow-up in order to pinpoint the risk factors for adverse outcomes.

LIMITATIONS

The present study was constrained by its single center design, small sample size, & brief follow- up time.

Our findings need to be confirmed by more comparative studies with bigger sample sizes & longer follow- up in order to pinpoint the risk factors for adverse outcomes.

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