

ORIGINAL ARTICLE

The Effect of Inhaled Corticosteroid (ICS) on Hba1c & Blood Sugar Level in Children with Asthma

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ABSTRACT

Objective: To assess the effect of inhaled corticosteroids on blood sugar (fasting & post prandial) and HbA1c level in children with asthma.

Design: Hospital based cross-sectional comparative study.

Setting: Department of Pediatric Medicine, J.K. Lon Hospital, SMS Medical College, Jaipur.

Participant: Total 90 patients of 3-12 years age group were enrolled & 81 were evaluated for effects of ICS on carbohydrate metabolism, after applying inclusion and exclusion criteria.

Results: The difference in mean Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS) and HbA1c level before and after 6 months of ICS therapy were statistically significant ($p < 0.001$) in the children studied. In our study, we found that recipient of low dose ($n=21$) and medium dose ($n=53$) ICS therapy did not show statistically significant changes in FBS ($p=0.178$ and $p=0.09$), PPBS ($p=0.072$ and $p=0.053$) and HbA1c ($p=0.278$ and $p=0.076$). However, recipient of the high dose ($n=7$) corticosteroids children showed statistically significant changes in FBS ($p=0.029$), PPBS ($p=0.012$) and HbA1c ($p=0.013$) after ICS therapy.

Conclusion: Low and medium dose ICS therapy ($< 400 \mu\text{g}$ per day) in children was not associated with significant alteration in glucose metabolism and can be safely used in children for treatment of asthma even for longer periods, whereas children on high dose ICS therapy ($> 400 \mu\text{g}$ per day), showed significant alteration in the glucose metabolism indices. Therefore, a caution should be observed while treating asthmatic children with high dose ICS and these children need continuous

monitoring for various side effects including alteration in glucose metabolism. However, a large sample size and longer duration of study is desirable for further recommendation.

Keywords: Asthma; Blood sugar; Inhaled Corticosteroid; Glycosylated hemoglobin.

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by recurrent airway obstruction, bronchial hyper-responsiveness and inflammation. It is one of the common chronic diseases in children worldwide¹. The prevalence of childhood bronchial asthma varies from 4 to 32% in different geographical areas². Various studies have estimated the prevalence of bronchial asthma to be 5-30% in pediatric population belonging to different backgrounds in India^{3,4}.

Inhaled corticosteroids are the first line anti-inflammatory therapy in asthma management. Hence, the early use of inhaled corticosteroids (ICS) has been advocated for optimal treatment of bronchial asthma⁵.

With long term use of corticosteroids, there is propensity for various side effects. The side effects of oral corticosteroids on metabolism are well documented, which is not the case with ICS.

However, long term use of ICS leads to various side effects, mainly due to faulty technique of its intake leading to its deposition in oropharynx. The side effects of inhaled corticosteroids can be broadly classified in to systemic side effects and local side effects. Systemic side effects include HPA suppression, adrenal insufficiency, decreased bone mineral density, cataract, glaucoma, effect on indices of carbohydrate metabolism (glycosylated hemoglobin and blood sugar level),

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whereas local side effects include dysphonia, pharyngitis, bronchospasm, reflex cough, oropharyngeal candidiasis⁶. In view of the paucity of studies in relation to this subject and some conflicting reports, this study was planned to evaluate the alterations in the carbohydrate metabolism (glycemic hemoglobin and blood sugar level) due to long term use of ICS.

AIMS AND OBJECTIVES

Aim: The primary purpose of the study was to assess the effect of inhaled corticosteroids on blood sugar (fasting and post prandial) and HbA1c level in children with asthma.

Objectives: The main objectives of the study were-

1. To assess the alteration in glycosylated hemoglobin (HbA1c) level with different dosages of ICS in asthmatic children;
2. To assess the alteration in fasting and postprandial blood sugar (PPBS) with different dosages of ICS in asthmatic children.

MATERIAL AND METHODS

Study design: Hospital based observational Study.

Ethical clearance: Approved by the Institutional Ethical Committee of SMS Medical College, Jaipur, Rajasthan.

Study Period: From June 2019 to October 2020.

Place of the Study: Department of Paediatric Medicine, J.K Lon Hospital, SMS Medical College, Jaipur, Rajasthan.

Study Population: Patients with newly diagnosed asthma (as per GINA Guideline), attending pulmonology clinic of J.K Lon Hospital, Jaipur were enrolled in the study after applying the exclusion and inclusion criteria.

Patient Selection: Total 90 pediatric patients attending pulmonology clinic of J.K Lon Hospital, Jaipur with newly diagnosed clinical asthma were enrolled in the study and finally 81 patients were evaluated for the effects of ICS on carbohydrate metabolism after applying the exclusion criterion.

Inclusion criterion:

Children of 3 to 12 years age group with newly diagnosed asthma, who are likely to be treated with inhaled corticosteroids as per GINA Guidelines⁷.

Prior Informed Consent.

Exclusion criterion:

- Patients with co-morbid diseases like cardiac disorders, pulmonary tuberculosis, diabetes, endocrinopathies and any other chronic disease and immunosuppression.
- Children on oral or systemic glucocorticoids.
- Children who were not compliant with inhaled corticosteroids therapy.

All children who were enrolled in study were investigated for baseline glycosylated hemoglobin (HbA1c), fasting and Postprandial Blood Sugar (PPBS) at their first visit. After completing 6 months of ICS therapy, again, fasting and two hour post prandial blood sugar & HbA1c were measured.

Fasting blood sugar after appropriate fasting was measured by finger prick test in the morning and repeated after 2 hours of breakfast by Abbott freestyle optium neo glucometer.

Cumulative doses of inhaled corticosteroids received by each child were calculated after the completion of 6 months of follow up.

Calculation of Sample Size & Statistical Analysis:

Sample Size: Sample size was calculated at 80% study power at α error of 0.05, and 95% confidence level assuming a detectable difference of at least 0.12 mg% HbA1c level before and after treatment with ICS in asthmatic children between 3 and 12-years of age as per the reference study. The required sample size was 81 subjects. Considering at least 10% loss to follow up or drop outs 90 subjects were enrolled in the present study.

Statistical Analysis: Normal and abnormal values were differentiated based on the American Diabetes Association cut off values of HbA1c levels. Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 23. Data were expressed in its frequency and its percentage as well as Mean and Standard Deviation. To elucidate the associations and comparisons between different parameters Chi-square (χ^2) test was used as nonparametric test. Student's T-test was used to compare the mean values between two groups and diverse groups. Initial and follow-up, two groups of HbA1c and ICS administrations were compared using paired and unpaired T- test. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant.

RESULTS

The Effect of Inhaled Corticosteroid (ICS) on HbA1c & Blood Sugar Level in Children with Asthma

42.22% of children were of 3-5-years age group, while 36.66% of children were of 8-12 years age group. The mean age of studied population was 6.88±3.06 years. 73.3% children were male, while 26.7% children were female. 55.6% children had family history of asthma/allergy.

Low, medium and high doses of ICS were categorized as per GINA guideline 2020⁷. During this study period, 21(25.92%) children received low dose of ICS, while 53(65.43%) children received medium dose of ICS. High dose of ICS was received by 7(8.65%) children.

Difference between baseline mean fasting (80.37mg/dl) blood sugar & fasting blood sugar at the end of follow-up after 6 months of ICS therapy(83.23mg/dl) was statistically significant(<0.001).

Difference between baseline mean postprandial blood sugar (94.67 mg/dl) & mean post prandial blood sugar at the end of follow-up after 6 months of ICS therapy (99.2mg/dl) was statistically significant (p<0.001).

Difference between baseline mean glycosylated hemoglobin (4.39 %) and mean glycosylated hemoglobin at the end of follow-up after 6 months of ICS therapy (4.58%) was statistically significant (p<0.001).

Table 1: Effect of Cumulative Inhaled Corticosteroids Dose (< 60 mg) on FBS, PPBS & HbA1C

PARAMETER	Baseline (mean value)		After 6months of ICS therapy (mean value)		P value
	Mean	SD	Mean	SD	
FBS (mg/dl)	78.67	5.25	80.57	3.63	0.178 (NS)
PPBS (mg/dl)	92.47	4.91	96.0	3.75	0.072 (NS)
HbA1c (%)	4.26	0.22	4.33	0.22	0.278 (NS)

Cumulative ICS dose of < 60 mg (budesonide) was not associated with statistically significant changes in FBS, PPBS and HbA1c at follow up (Table 1).

Table 2: Effect of Cumulative ICS Dose (61-120 mg) on FBS, PPBS & HbA1c

PARAMETER	Baseline (mean value)		After 6months of ICS therapy (mean value)		P value
	Mean	SD	Mean	SD	
FBS (mg/dl)	80.81	5.68	83.67	5.24	0.09 (NS)
PPBS (mg/dl)	95.32	6.70	99.96	6.66	0.053(NS)
HbA1c (%)	4.5	0.33	4.66	0.30	0.076 (NS)

Cumulative ICS (budesonide) dose of 60-120 mg was not associated with statistically significant changes in FBS, PPBS and HbA1c at follow-up (Table 2).

Table 3: Effect of ICS Dose (>120 mg) on FBS, PPBS & HbA1c

PARAMETER	Baseline (mean value)		After 6months of ICS therapy (mean value)		P value
	Mean	SD	Mean	SD	
FBS (mg/dl)	82.14	3.88	87.86	5.31	0.029 (S)
PPBS (mg/dl)	96.28	4.83	103.0	4.54	0.012 (S)
HbA1c (%)	4.54	0.24	5.1	0.50	0.013 (S)

Cumulative ICS (budesonide) dose of >120 mg was associated with statistically significant changes in FBS, PPBS and HbA1c at follow-up (Table 3).

Table 4: Association between HbA1c and Dosage of ICS Administration

ICS Dose	Average ICSdose/day	Normal risk children (HbA1c<5.7 mg%)	High risk children (HbA1c 5.7-6.4 mg%)	Total
Low dose	216µg	21(100%)	0	21
Medium dose	389µg	53(100%)	0	53
High dose	720µg	5(71.4%)	2(28.57%)	7
p value	p<0.001 (S)			

At the end of 6 months of follow-up, out of total 7 children who received high dose of ICS, only 2 children were associated with high risk HbA1c level (5.7-6.4 mg%) & none of the children had HbA1C in diabetic range (>6.5%) (p<0.001). Cumulative& average daily dose of inhaled corticosteroids received by both high-risk children were 147mg, 161mg, 820µg, & 894µg respectively (Table 4).

DISCUSSION

The present study was a hospital based observational study, made in the Department of Paediatric Medicine, J. K Lon Hospital, SMS Medical College Jaipur. Total 90 asthmatic children were enrolled in the study & finally 81 patients were evaluated for effects of ICS therapy on carbohydrate metabolism after applying exclusion criteria.

All children were treated with different dosage regimen (low, medium or high dose) of ICS therapy as per

GINA guidelines 2020. Minimum follow up duration was 6 months after start of treatment with ICS.

Baseline mean fasting and Post Prandial Blood Sugar (PPBS) were 80.37 mg/dl and 94.67 mg/dl respectively and after 6 months of ICS therapy, mean fasting & post prandial blood sugar values were 83.23 mg/dl and 99.2 mg/dl respectively. The difference in FBS and PPBS before and after 6 months of ICS therapy was statistically significant (p<0.001). Similar was the observation made by Daniel et al. in their study⁸.

Statistically significant difference was noted between baseline mean glycosylated haemoglobin (4.39 %) & mean glycosylated haemoglobin (4.58%) at follow-up after 6 months of ICS therapy in our study. In the study made by Daniel et al., there was a statistically significant (p<0.001) difference in mean glycosylated hemoglobin level (5.13%) after ICS therapy for a minimum 6 months period as compared to the baseline value (4.98%)⁸.

A similar study was made by *Wasim et al.*, who concluded that there was a statistically significant difference in the mean HbA1c level before & after 6 months of moderate dose of inhaled corticosteroid in children of age group 5-15 years⁹.

In our study, total 21 (25.92%) children received low dose steroids (cumulative dose of ICS < 60 mg and average 216µg budesonide per day) but it was not associated with statistically significant changes in FBS (p=0.178), PPBS (p=0.072) and HbA1c (p=0.278) level.

Another group of 53 (65.43%) children received medium dose ICS (cumulative ICS dose 60-120 mg and average 389 µg budesonide per day) and it was also not associated with statistically significant changes in FBS (p=0.09), PPBS (p=0.053) and HbA1c (p=0.076) level.

Remaining 7 (8.65%) children received high dose ICS (cumulative ICS dose >120 mg and average 720 µg budesonide per day). Recipient of high dose inhaled corticosteroids group showed statistically significant changes in FBS (p=0.029), PPBS (p=0.012) and HbA1c (p=0.013).

In our study, 2 out of 90 children were associated with high risk HbA1c level (>5.7%) at the end of 6 months of follow-up. These children with high risk HbA1c level receive high dose ICS therapy during their treatment. Similarly, the study made by *Danielet al.* & *Kaarthikeyaniet al.*, concluded that higher cumulative dose of inhaled steroids was associated with higher HbA1c level^{8,10}.

Contrary to our study, *Bindusha et al.*, concluded that the difference in mean HbA1c (p=0.305) and FBS (p=0.447) was due to either low dose (n=83) or high dose (n=102) of ICS at the end of 6 months of follow-up, which were statistically not significant¹¹. This contradiction to our study may be due to fact that the base line mean FBS and HbA1c level were not available with them.

Limitation of the our study was its small sample size & children (study subject) could not be closely followed up, compliant and monitored adequately due to COVID-19 pandemic.

CONCLUSION

On the basis of our study, we conclude that low and medium dose ICS therapy (< 400 µg per day) in children was not associated with significant alteration in glucose metabolism and it could be safely used in children for treatment of asthma even for longer periods, whereas

children on high dose ICS therapy (> 400 µg per day) showed significant alteration in the glucose metabolism indices. Therefore, a caution should be taken while treating asthmatic children with high dose ICS and these children need continuous monitoring for various side effects including alteration in glucose metabolism. However, a large sample size and longer duration of the study is desirable for further recommendation.

Contribution: Sharma BS conceived & designed the study & revised the manuscript for important intellectual content. He will act as guarantor of the study. Agarwal Vishnu & Kumar Virendra collected data & drafted the paper. Kumar Virendra evaluated the patient with the help of investigation. Agarwal Vishnu analyzed the data & helped in manuscript writing. The final manuscript was approved by all authors.

Key message- What is Already Known- Long term use of ICS is also associated with various side effects.

What this study adds- Low and Medium dose ICS therapy (< 400 µg per day) in children is not associated with significant alteration in glucose metabolism.

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