International Journal of Contemporary Pediatrics
Daniel S et al. Int J Contemp Pediatr. 2017 May;4(3):796-800
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20171489

Original Research Article

A study on HbA1c profile in children with asthma using inhaled corticosteroids

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Received: 14 March 2017
Accepted: 25 March 2017

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ABSTRACT

Background: Inhaled corticosteroids (ICS) are the mainstay of treatment for persistent bronchial asthma in children. Even though ICS is comparatively safe, few systemic toxicities have been reported. We have conducted a study on HbA1c profile of 170 asthmatic children who are on ICS for atleast 6 months. Glycosylated hemoglobin (HbA1c), fasting blood sugar (FBS), Postprandial blood sugar (PPBS) levels were measured before initiating ICS and after 6 months using venous blood samples. HbA1c measured using immunoassay. The objective of the study was to detect prevalence of significant hyperglycemia among children with asthma who are on inhaled corticosteroids. Study design used as a prospective follow up study, setting of the study was to Pediatric asthma clinic, Govt. TDMCH, Alappuzha, Study population used Children between 3 to 12 years attending pediatric asthma clinic.
Methods: Cumulative doses of ICS and bronchodialators were measured by providing an asthma diary to mark the dose of medication. FBS, PPBS, and HbA1c levels were measured before initiating ICS and after 6 months. To elucidate the assosiations comparisons between different parameters Chi-square test was used as non-parametric test. Student's T- test was used to compare mean values between 2 groups and different groups. Initial and follow up two groups of HbA1c and ICS administrations were compared using paired and unpaired T-test.
Results: There is a significant increase in the mean HbA1c of the total study population before and after treatment with ICS.
Conclusions: Long term use of ICS can affect glucose metabolism of asthmatic children.

Keywords: Bronchial asthma, HbA1c, Inhaled corticosteroids

INTRODUCTION

The National Asthma Education and Prevention Program (NAEPP) guidelines recommended daily ICS as treatment of choice for all patients with persistent asthma. Although ICS therapy has been widely used in adults with persistent asthma, its application in children has lagged due to concerns of the potential for adverse effects with chronic use. Generally, clinically significant adverse effects that occur with chronic systemic corticosteroids therapy have not been seen or have been only very rarely reported in children receiving ICSs in recommended doses. The risk effects from ICS therapy is related to the dose and frequency with which ICSs are given. High doses (≥1000µgm/day in children) and frequent administration (4 times daily) are more likely to cause local and systemic adverse effects.[1]

Inhaled glucocorticosteroids are absorbed from the lung, accounting for some degree of systemic bioavailability. The risk of systemic adverse effects from an inhaled glucocorticosteroid depends upon its dose and potency,

the delivery system, systemic bioavailability, first pass metabolism (conversion to inactive metabolites) in the liver, and half-life of the fraction of systemically absorbed drug (from the lung and possibly gut). Therefore, systemic effects differ among the various inhaled glucocoticosteroids. Several comparative studies have demonstrated that ciclesonide, budesonide, and fluticasone propionate at equipotent doses have less systemic effect. Current evidence suggests that in adults, systemic effects of inhaled glucocorticosteroids are not a problem at doses of 400microgram or less budesonide or equivalent daily.

Glycosylated hemoglobin (HbA1c)

HbA1c levels provide an indication of the average blood glucose concentration during the preceding 2-3 months. Glucose sticks to the hemoglobin to make a glycosylated hemoglobin molecule. It is formed in a non-enzymatic glycation pathway by hemoglobin exposure to plasma glucose. Normal levels of glucose produce a normal amount of HbA1c. As the average amount of plasma glucose increases the fraction of glycosylated hemoglobin increase in a predictable way. This serves as a marker for average levels over the previous months prior to measure. A child without diabetes normally will have an A1c level between 4-6%. The 2010 American Diabetes Association (ADA) standards of medical care in diabetes added the HbA1c more than 6.5% as another criterion for diagnosis of diabetes. It also recognized the use of HbA1c to identify people at risk of developing the diabetes in future known as pre-diabetes.

In a study published in March 4, 2010, issue of New England journal of medicine, people with HbA1c level between 5-5.5% were identified as being within normal ranges. With each incremental HbA1c increase, the incidence of diabetes increased as well, those at a level of 6.5% or greater considered diabetic and between 6-6.5% are considered at a very high risk (9 times greater than the normal range) for developing diabetes. The HbA1c test has low variability from day to day, levels are not as affected by stress and illness, it has greater stability and the patient is not required to fast before the test is performed

The revised ADA guidelines classify people with HbA1c levels in the range of 5.7-6.4% as at very high risk for developing diabetes over 5 years. The range 5.5-6% according to the ADA guidelines is the appropriate level to initiate preventive measures. Although the normative distribution for HbA1c levels has been described and standardized for adults, normal ranges for children have not been established. In a study conducted by Third National Health and Nutrition Examination Survey, the mean HbA 1c level in children was found to be 4.99% (SD 0.50%).[2] HbA1c is actually influenced by both life span of the erythrocyte and its permeability to glucose. Differences in HbA1c may reflect higher average glycemia over the preceding 2-3 months (which may also be physiological and within normal limits), or the differences may reflect some level of relative insulin resistance. Indeed, an elevated HbA1c level has been associated with excess mortality risk in the general population.

Measurements of glycosylated hemoglobin more accurately identify persons at risk for clinical outcomes than the commonly used measurement of fasting glucose, according to a study by researchers at the Johns Hopkins school of public health. HbA1c accurately predict future diabetes, and they better predict stroke and heart disease.[3]

Fasting blood sugar (FBS) and postprandial blood sugar (PPBS)

Fasting blood sugar is taken as the venous blood sugar level and the expected range in a child is 60-100mg/dl. This value is dependent on the body insulin level and peripheral utilization of glucose. In the postprandial blood sugar, blood is taken 2 hours after the last level. In this, the blood sugar can go high according to the meal in the first hour following the meal. The usual PPBS value is <120mg/dl.

METHODS

Inclusion criteria

Children who are diagnosed to have persistent asthma according to GINA report guidelines who are started on long term prophylaxis with inhaled corticosteroids. Both controlled and uncontrolled asthmatic children were eligible for the study.

Exclusion criteria

Children who are on oral corticosteroids and those having co-existing pulmonary, cardiac, renal, hepatic and endocrine diseases were excluded.

The parents of patients were provided with a questionnaire regarding family and personal history of asthma and atopic disease and presence of diabetes in 1st and 2nd degree relatives. Cumulative doses of inhaled corticosteroids (budenoside) and bronchodilators (inhaled beta 2 agonists) were measured by providing an asthma diary to mark the dose of medication. Glycosylated hemoglobin (HbA1c), fasting blood sugar (FBS), post prandial blood sugar (PPBS) levels were measured before initiating inhaled corticosteroids (ICS) and after 6 months using venous blood samples. Blood samples were collected in the early morning under fasting conditions and 2 hours after breakfast. HbA1c measured using immunoassay.

Analysis

Normal and abnormal values were differentiated based on American Diabetes Association cut off values of HbA1c

levels. Data were analysed using computer software, Statistical Package for Social Sciences(SPSS) version 10. Data are 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 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

Analysis of the data collected from 170 asthmatic children between 3-12 years of age attending Pediatric Asthma clinic was made as given in Table 1. Among the study population 48.2% of children belonged to mild persistent asthma (ICS cumulative dose=18000-36000) and 51.8% belonged to moderate persistent asthma (ICS cumulative dose=36001-72000).

Table 1: Dosage distribution of ICS.

ICS dosage	Frequency	Percent
Low dose	82	48.2
Medium dose	88	51.8
Total	**170**	**100**

Among study population 96.5% of children had normal HbA1c (< 5.5mg%) and 6 children (3.5%) had HbA1c in the high-risk range (5.5-6.4mg%).

Table 2: Distribution of HbA1c in study population.

HbA1C	Frequency	Percent
Normal (<5.5 mg%)	164	96.5
High risk (5.5 - 6.4 mg%)	6	3.5
Total	**170**	**100**

Table 3 shows a highly significant (p<0.001) increase of FBS and PPBS after 6 months of treatment with inhaled corticosteroids (ICS).

Table 3: Distribution of mean FBS (mg/dl) and PPBS (mg/dl) among study population before and after treatment.

Parameters	Group	Mean	± SD	t value	p value
FBS (mg/dl)	Initial	81.10	7.51	- 4.216	< 0.001
	Follow up (after 6 Months)	83.15	5.27		
PPBS (mg/dl)	Initial	92.34	6.91	- 11.876	< 0.001
	Follow up (after 6 Months)	97.01	5.45		

Table 4: Mean HbA1c of study population before and after treatment.

Parameters	Group	Mean	± SD	t value	p value
HbA1C (mg%)	Initial	4.98	0.38	- 12.903	< 0.001
	Follow up (after 6 Months)	5.13	0.38		

Table 5: Association between follow up HbA1C (after 6 months) and age.

Age	Follow up HbA1C (after 6 months)		Total
	Normal	**High risk**	
3 - 6	83		83
	50.60%		48.80%
6 - 9	42	1	43
	25.60%	16.70%	25.30%
9 - 12	39	5	44
	23.80%	83.30%	25.90%
Total	**164**	**6**	**170**

Chi Square: 11.151; P < 0.01

There is a highly significant increase in the mean HbA1c of total study population after treatment. The initial mean HbA1c was 4.98 and at the end of 6 months it is 5.13.

In the Table 5, it is shown that none of the children in the 3-6 years' age group had high risk HbA1c and 83.3% of children in the high risk HbA1c group belonged to the age group of 9-12 years. From this it is evident that as the age advances the metabolic effects following ICS administration increases.

Table 6: Association between follow up HbA1c and dosage of ICS administration.

ICS administration	Follow Up HbA1C (after 6 months)		Total
	Normal	**High risk**	
Low dose (mild)	82		82
	50.00%		48.20%
Medium dose (moderate)	82	6	88
	50.00%	100.00%	51.80%
Total	**164**	**6**	**170**

Chi Square: 5.795; P < 0.05

None of the children taking low dose of ICS have HbA1c in the high-risk group. All the children in high-risk HbA1c group are on medium dose of ICS.

There is a significant increase in follow up HbA1c, both in mild and moderate asthmatic children using low and medium dose inhaled corticosteroid.

Table 7: Mean HbA1c of children using low and medium dose ICS.

HbA1C Initial	**Mild**	**4.77**	**0.35**	**-7.935 (t value)**	**<0.001 (p value)**
	Moderate	5.17	0.29		
HbA1C After 6 Months	Mild	4.93	0.35	-8.083 (t value)	<0.001 (p value)
	Moderate	5.33	0.30		

In Table 8, it is shown that 6.8% of children using medium dose ICS has high-risk HbA1c values. It shows that higher the dose of ICS more the risk for abnormal HbA1c.

Table 8: Association between ICS administration and follow up HbA1c.

Follow Up HbA1C (after 6 months)	ICS administration		
	Mild (low)	**Moderate (medium)**	**Total**
Normal (< 5.5)	82	82	164
	100.00%	93.20%	96.50%
High risk (5.5 - 6.4)		6	6
		6.80%	3.50%
Total	**82**	**88**	**170**

Chi Square: 5.795; P < 0.05

DISCUSSION

Inhaled corticosteroids are the preferred treatment in children of all ages with persistent asthma. Chronic use of ICS improves long term outcomes for children of all ages with mild or moderate persistent asthma. However chronic use of ICS may result in adverse systemic effects. In this study, there is a significant increase in HbA1c levels of children with mild and moderate persistent asthma, who are using low and medium dose of ICS respectively. In a study by Oya et al also showed a significant increase in HbA1c of asthmatic children, when compared to normal children.[4]

Many studies researching oral or high dose ICS are found in literature. Systemic adverse effects of administration of ICS are emphasized in these studies, but there remains a certain degree of uncertainity concerning the effects of long term administration of low doses. In the study by Oya Yucel HbA1c levels were found to be higher in asthmatic children than healthy controls. The findings also showed that the effects of two medicines (budenoside and fluticasone propionate) on the blood glucose at prophylactic doses are similar.[4] Sathiyapriya, et al showed that HbA1c concentrations increased significantly in the non-diabetic adult patients with asthma.[5]

In addition to steroids, the use of beta-2 agonists for acute asthma and the severity of illness can also influence the glucose metabolism. However, studies in adult asthmatics have documented beneficial effects of ICS on carbohydrate metabolism. Kiviranta and Turpeinen demonstrated that the antiasthmatic effect of high dose belcomethasone dipropionate and budesonide was accompanied by a significant initial decrease in insulin resistance with a parallel improvement in glucose tolerance.[6] During the prolonged treatment, a small increase in insulin sensitivity was found.[6]

Pediatric studies on the effects of ICS on carbohydrate metabolism are scant. Turpeinen, observed the antiasthmatic and metabolic effects of budesonide inhalations in initially high (800 microgram for one month) and subsequently lower (400 microgram for 4 months) dosage in nine children with asthma, aged 5-10 years.[7] They observed that the high dosage increased significantly the ratio of serum insulin to blood glucose (a marker of insulin sensitivity) after lower dosage, the ratio declined significantly to 13.5mU/mmol. The dose of 400 micrograms for 4 months did not have any significant effects.

In a previous study on 15 asthmatic children treated with inhaled beclomethasone dipropionate (mean 490 microgram/day) and 11 asthmatic control subjects receiving no corticosteroid therapy measurements of 24-h urinary free cortisol and 17 hydroxy corticosteroids, serum cortisol, response to ACTH, and the oral metyrapone test showed no significant difference between the two groups. All the results were within normal limits, and carbohydrate metabolism, as shown by blood glucose and HbA1c, was not affected by beclomethasone.[8]

Long term use of ICS in children with asthma may be associated with a variety of side effects, similar to those observed with systemic corticosteroid therapy. The average blood glucose level can be affected in children using prophylactic doses of ICS. The development of adverse effects of ICS therapy is dependent on the dose, frequency and duration of these drugs.[9] Limited pharmacokinetic data are available to define the pulmonary absorption characteristics of budenoside. Evidence from a population analysis shows that the pulmonary absorption of budenoside is prolonged and has wide inter individual variation.[10,11] Brurche et al investigated the absorption of ICS in patients with different severities of asthma receiving different doses.[12] Systemic availability of fluticasone propionate was found to be substantially less in patients with moderate to severe asthma than in healthy controls. Although fluticasone propionate and budenoside are widely used, they are not without systemic side effects.

The present study showed that there is a significant increase in mean HbA1c of total study population before (mean HbA1c=4.98%) and after (mean HbA1c=5.13%) treatment with inhaled corticosteroids. It is also found that higher the dose of ICS more the risk for abnormal HbA1c.

CONCLUSION

The present study was an attempt to assess the HbA1c levels in children with asthma using inhaled corticosteroids in prophylactic doses. The study has brought out some significant conclusions, which are summarized below.

- Majority of patients (51.8%) in the study population belonged to moderate persistent asthma using medium dose (cumulative dose of ICS = 36001-72000µgm of budenoside MDI) 48.2% are using low dose ICS (cumulative dose of ICS = 18000-36000µgm of budenoside MDI).
- There is a significant increase in the follow up fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) values in the study population, even though the mean value is in the normal range.
- Among 170 children in the study population 6 children (3.5%) had HbA1c in the high-risk range (5.5-6.4%).
- All 6 children in the high-risk HbA1c group are above 6 years of age, showing that higher the age more the risk for abnormal HbA1c.
- There is a significant increase in the mean HbA1c of the total study population before (mean-4.98%) and after (mean-5.13%) treatment with ICS.
- Higher the dosage of ICS, more is the risk for abnormal HbA1c.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Daniel S, Jose O. A study on HbA1c profile in children with asthma using inhaled corticosteroids. Int J Contemp Pediatr 2017;4:796-800.