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Original Article

Paediatrics Section

HbA1c Levels in Children with Persistent Asthma on Inhaled Corticoids: A Descriptive Cohort Study

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ABSTRACT

Introduction: Asthma is one of the most common chronic respiratory conditions in children. Inhaled corticoids have revolutionised the treatment of asthma but long-term inhaled and systemic corticoids have been shown to have an effect on glucose metabolism.

Aim: To compare the glycosylated haemoglobin (HbA1C) levels in children with asthma on Inhaled Corticosteroids (ICS) for less than 6 months with that of children on ICS for 1-6 months.

Materials and Methods: The study was a descriptive cohort study done in the Paediatric Asthma clinic in a tertiary care teaching hospital in Southern India. Authors enrolled 75 children aged 1-18 years with persistent asthma (GINA guidelines) on inhaled corticosteroids for six months or more (cases) and another 75 age-matched children on inhaled corticosteroids for 1-6 months (controls). The HbA1c levels in the two groups and its relationship with cumulative dose of ICS was analysed. Various clinical factors were compared using chi-square test. Mean HbA1c levels between the two groups were compared using Student's t-test.

Results: Among the children studied, 7 (9.3%) of cases and none of controls had elevated HbA1C levels above 6%. The difference was statistically significant (p-value=0.0067). The Mean HbA1C level in cases was 5.27 and 5.07 in controls. The difference was statistically significant (p-value=0.007). There was an increase in HbA1c levels with increase in total cumulative dose of steroids (Coefficient of correlation 0.23).

Conclusion: HbA1c levels become significantly higher in children on inhaled corticosteroids for more than six months. Hence glycaemic status needs to be monitored in all children on long-term inhaled corticosteroids.

Keywords: Bronchial asthma, Glycated haemoglobin, Hyperglycaemia

INTRODUCTION

Inhaled Corticosteroids (ICS) have revolutionised the treatment of persistent asthma by reducing airway inflammation and hyper-responsiveness [1-3]. National /international guidelines recommend low dose ICS as the first line preventer therapy for mild persistent asthma and medium dose ICS with/without Long-Acting Beta Agonists (LABA) for moderate persistent asthma [4,5]. Long-term systemic steroid therapy is known to cause hyperglycaemia and the adverse effects of hyperglycaemia are well documented [6]. Glucocorticoids cause hyperglycaemia by increased gluconeogenesis and decreased glucose uptake in the liver and adipocytes by reduced insulin binding. Long-term use of Inhaled Corticosteroids has also been shown to have effects on glucose metabolism in adults but studies in children with asthma are rare [7-10]. Measurement of HbA1c level is useful to assess the average blood glucose concentration in the previous 8-12 weeks [11].

The present study aimed to the effect of long-term inhaled corticosteroids on blood HbA1c levels in children with persistent asthma (GINA guidelines) [12].

MATERIALS AND METHODS

Study setting: This descriptive cohort study was conducted in the Paediatric Asthma Clinic at Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, India a tertiary care teaching hospital in South India from September 2014 to September 2016 after clearance by the institutional ethics committee (IEC Reference number – CSP – MED/14/SEP/18/160).

Participants: Children between the ages of 1-18 years, with persistent asthma on ICS with correct technique and good compliance (defined as taking inhaler as prescribed on at least 20/30 days in a month) were enrolled. Children with asthma on ICS for more than six months were the cases and those on ICS for 1-6 months were controls. Informed consent was obtained from all parents and assent from participants in above 14 years of age.

Children who had received oral corticosteroids for >14 days in the preceding four weeks, those with co-existing systemic illness and those not willing for participation were excluded. Children with clinical pallor, splenomegaly were excluded.

Sample size: Based upon a previous study [13], where the mean difference was 0.3, using two samples mean test with power of 80%, α error 5%, the minimum sample size required for the study was 64 in each arm. However, 75 children were included to consider for dropouts.

Children were enrolled according to the inclusion/exclusion criteria. Demographic details, history and physical examination findings were noted in the study proforma. Weight was measured using a digital weighing scale. For children above two years standing height was measured using stadiometer and for children less than two years supine length using infantometer. The blood pressure was recorded using a sphygmomanometer with age-appropriate cuffs. Normal values were defined as systolic and diastolic blood pressure values between 50th and 90th centile for the given height, sex and age. Participants were assigned into case and control groups depending on the duration for which they were using regular ICS. Cumulative doses of ICS were calculated by the number of used canisters as reported by the parents, prescription verification and the number of doses remaining in the canisters partially used.

Specimen collection and handling: A 3 mL whole blood was collected in vacuum collection tube containing EDTA. HbA1C levels were measured using D-10 Haemoglobin Program.

Operative definitions

- Normal HbA1C < 6% (Nelson 20th Ed) [14].
- Steroid dose as per GINA guidelines [12] depicted in [Table/Fig-1] and Expert panel report-3 [3].

	Adolescents (>11 years)			Children 6-11 years		
Inhaled corticosteroid	Low	Medium	High	Low	Medium	High
Budesonide	200-400	>400-800	>800	100-200	>200-400	>400
Fluticasone propionate	100-250	>250-500	>500	100-200	>200-400	>400

[Table/Fig-1]: Steroid dose as per GINA guidelines.
*Low, medium and high doses of inhaled corticosteroid (mcg)according to GINA guidelines 2015

STATISTICAL ANALYSIS

HbA1c levels in the two groups and its relationship with cumulative dose of ICS was the primary outcome measured. Data are expressed in its frequency and percentages as well as mean and standard deviation. To interpret the associations and comparisons between various parameters chi-square test was used. Mean HbA1c levels between the two groups were compared using Student's t-test. A p-value of <0.05 was considered statistically significant. IBM SPSS version 16.0 was used for statistical analysis.

RESULTS

A total of 150 children with moderate persistent asthma were enrolled in the study. Among the 75 cases, 54 (72%) were on inhaled corticosteroids for 6-12 months and 21 (28%) were on inhaled corticosteroids for >12 months. Maximum duration of inhaled steroid was 18 months.

In the control group, 45 (60%) children were on ICS for 1-3 months and 30 (40%) children on ICS between >3 to <6 months.

The age, gender, asthma severity at diagnosis and type of ICS used in the two groups were comparable [Table/Fig-2].

		Cases		Controls		Total		p-value
Age		N	(%)	N	(%)	N	(%)	
1-3 years		7	9.3%	2	2.7%	9	6%	
4-6 years		16	21.3%	14	18.7%	30	20%	0.120
7-10 years		17	22.7%	28	37.3%	45	30%	
11-18 years		35	46.7%	31	41.3%	66	44%	
Gender		N	%	N	%	N	%	
Boys		55	73.3%	46	61.3%	101	67.3%	0.117
Girls		20	26.7%	29	38.7%	49	32.7%	
Asthma severity		N	%	N	%	N	%	
Mild persistent asthma		17	22.7%	13	17.3%	30	20%	0.414
Moderate persistent asthma		58	77.3%	62	82.7%	120	80%	
Steroid dose		N	%	N	%	N	%	
B	Medium	68	90.7%	72	96%	140	93.3%	0.19
F	High	7	9.3%	3	4%	10	6.6%	
Total		75	100%	75	100%	150	100%	

[Table/Fig-2]: Ages, gender, asthma severity at diagnosis and type of ICS in the two groups.
B: Budesonide; F: Fluticasone; *Chi-square test was applied

All children on budesonide were getting medium dose and those on fluticasone were getting high dose.

The number of obese children was significantly more in the cases group 13% (10) versus 2.7% (2) (p-value=0.0089), but none of these obese children both in the cases and control group had altered HbA1c values. The [Table/Fig-3] gives the nutritional status (BMI) of children in the two groups. All children who participated in the study were found to be normotensive.

As depicted in [Table/Fig-4], 9.3% of cases had elevated HbA1C levels above 6%. Maximum HbA1C level was 6.2%. The difference was statistically significant. (p-value=0.0067). The Mean HbA1C level in cases was significantly more (5.27 vs 5.07) than controls. (p-value=0.007).

BMI	Cases	%	Controls	%	Total	%
Normal	64	85.3%	73	97.3%	137	91.3%
Overweight/ obese	10	13.3%	2	2.7%	12	8%
Underweight	1	1.3%	0	0%	1	0.7%
Total	75	100%	75	100%	150	100%

[Table/Fig-3]: Body mass index.

HbA1C	Cases	%	Controls	%	p-value
4-6%	68	90.7%	75	100%	=0.0067
>6-7%	7	9.3%	0	0%	
Mean HbA1C (%) (Standard deviation)	5.27 (0.35)		5.07 (0.29)		0.007
Mean Blood glucose level (mg/dL) (Standard deviation)	107.61(11.52)		109.07 (13.7)		0.048

[Table/Fig-4]: HbA1C levels between both groups.
*Student t-test was applied

The [Table/Fig-5] depicts relationship between cumulative dose of ICS and elevation in HbA1c levels. When cumulative dose was below 95,999 mcg, no elevation of HbA1c was found. A 7.54% of children receiving a cumulative dose of 96,000-165,999 mcg and 15% of those receiving 166,000-265,000 mcg had elevated HbA1C levels. There was a weak positive correlation between cumulative dose of ICS and HbA1c levels with the coefficient of correlation being 0.23.

Cumulative dose	Cases N (%)	Controls N (%)	Hba1c	
			4-6%	>6-7%
<25 mg	0	18 (24%)	18	
26-45 mg	0	54 (72%)	54	
46-95 mg	2 (2.6%)	3 (4%)	5	
96-165 mg	53 (70.6%)	0	49	4
166-265 mg	20 (26.6%)	0	17	3
Total	75	75	143	7

[Table/Fig-5]: Relationship between cumulative dose and HbA1C.
r-value= 0.23

DISCUSSION

The systemic bioavailability of ICS is claimed to be minimal and therefore the metabolic complications related to ICS use is expected to be negligible. However, the systemic bioavailability depends on the type of molecule, the mode of administration, daily dose, cumulative dose and the pharmacokinetic and pharmacodynamic properties of ICS drug molecule. Despite developing various inhalation devices to improve locally targeted delivery to the airways, significant proportions can still reach the systemic circulation especially at high doses over long periods of time. Although the first pass metabolism (conversion to inactive metabolites) in the liver reduces the fraction, part of the ICS can be absorbed through the lungs and gastrointestinal tract [8,15].

Though it is believed that the adverse effects of systemic corticosteroids have been addressed by the introduction of inhalation therapy, reports of alteration in glucose metabolism even with inhaled corticosteroids when used for prolonged periods are appearing [13,16]. Glycosylated haemoglobin is a simple, objective test and is representative of average blood glucose concentrations over several weeks without being affected by short term fluctuation. The present study evaluated the effect of ICS on HbA1C levels in 150 children with persistent asthma of whom 75 had been on ICS for >6 months (cases) and 75 for 1-6 months (controls).

In the present study, 9.3% of children using ICS for >6 months had elevated HbA1c (>6%) p-value=0.0067. The mean HbA1C level in cases was significantly higher (5.27±0.35%) than among controls (5.07±0.29%) (p=0.007). There was no significant difference between the mean blood glucose levels in cases and controls indicating that

blood glucose alone are not a useful indicator (107.61±11.52 mg/dL versus 109.07±13.7 mg/dL). There was a positive correlation between cumulative doses of ICS and HbA1c levels in children with coefficient of correlation being 0.23. A cumulative dose of <95 mg of steroid was not associated with any elevation of HbA1c suggesting that those on low dose steroids for <4 months are not at risk.

Yucel O et al., studied 141 children with asthma using low dose ICS for >6 months and found that HbA1c levels were higher than in children without asthma (5.44 versus 5.14) (p=0.006) [17]. The mean blood glucose concentration was found to be 117 mg/dL in patients receiving ICS and 106 mg/dL in the control group. The difference was not statistically significant.

They concluded that this marginal increase in HbA1c levels was not of any clinical significance as the levels were well within the normal range (5-6%). Studies in adult patients stressed by uncontrolled asthma, the anti-asthmatic effect of high dose ICS caused significant improvement in glucose tolerance. They suggested that overall, ICS have a beneficial effect on glucose metabolism in patients with uncontrolled asthma [18,19].

Bindusha S et al., found no statistically significant difference was found between the mean HbA1c levels of the children using a low dose (6.013±1.185) and high dose inhaled steroids (6.206±1.365) for at least six months [20].

Though long-term ICS have been reported to cause systemic side effects including hypertension all the 150 children in the present study were normotensive.

In the present study, there were significantly more obese children among the cases and the mean BMI of the cases was significantly higher than that of the controls. Some authors have suggested that the cut-off levels of HbA1c in obese children should be lower (5.8%) because they are at higher risk of the adverse effects of hyperglycaemia [21]. Some studies have suggested that long-term inhaled corticosteroids can cause weight gain while others have shown modern pharmacological asthma treatment does not contribute much to the development of obesity in children [22,23]. The pretreatment weight was not consistently available for all patients in the present study. Further evaluation is required to determine whether the inherent obesity contributes to the alteration in HbA1c or whether the inhaled corticosteroid had any contribution.

LIMITATION

The limitation of the present study is the unavailability of HbA1C level and BMI prior to initiation of inhaled corticosteroids. The fasting, post prandial blood glucose levels and Hb% was not measured. The event rate in the control group suggests that a larger sample size will be required. More studies with long-term follow-up and a larger cohort is required to evaluate the presence of asymptomatic hyperglycaemia in asthmatic children on preventer therapy.

CONCLUSION

In conclusion, HbA1C levels were higher in children on Inhaled Corticosteroids for more than six months. Higher cumulative dose of inhaled steroids was associated with higher HbA1C levels. Hence, glycaemic status needs to be monitored in all children on long term Inhaled Corticosteroids particularly for those with other risk factors like family history of Diabetes, Obesity etc., for glucose intolerance.

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