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EFFECT OF LOW DOSE INHALED CORTICOSTEROIDS ON HBA1C AND FBS LEVELS IN CHILDREN WITH ASTHMA

Pediatrics

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ABSTRACT

Asthma is a chronic inflammatory condition associated with episodic airway obstruction, which is further exaggerated by various environmental triggers. Inhaled corticosteroids (ICS) are the preferred mainstay treatment in children with persistent asthma. Chronic use of ICS will not only improve long term outcome in asthmatic children, but also has some adverse systemic effects. Increase in blood glucose levels in asthmatic children on high doses of inhaled or oral corticosteroids have been emphasized by many studies. HbA1C levels and fasting blood glucose (FBS) provide an approximate estimate of average blood glucose. Very limited reports in literature have addressed the issue of long term glycemic levels in these children. The present study was conducted to know the HbA1c and FBS levels in children with persistent asthma on low dose ICS. **Objective:** To analyze and compare the HbA1c and FBS levels in children with asthma using low dose inhaled corticosteroids with non-asthmatic children. **Methodology:** A case control study conducted on 120 children aged between 3 to 14 years. Cases were divided into 2 groups, 60 cases included asthmatic children on low dose ICS for a minimum of 3 months duration and 60 controls included non-asthmatic children who were matched for age and sex. Children with diabetes, chronic diseases, and on oral steroid therapy were excluded. Data regarding age, sex, socio demographic profile, clinical examination at the time of presentation were collected in a prewritten proforma. HbA1c and FBS levels were measured in both the groups and results are compared. **Results:** The mean age of study group (n=60) was 85.1±36 months and comprised 28 females and 32 males. The mean HbA1c level in the study and control groups were 5.40±0.38 % and 5.31±0 (p value=0.2). The mean FBS level in the study and control groups were 86.63 ±10.32 mg/dl and 84.77± 11.1 mg/dl, respectively (p value=0.7). There was no significant correlation between cumulative dose of ICS and HbA1c levels. Similarly, HbA1c and FBS levels did not change with increased duration of usage of ICS. **Conclusion:** There was no significant difference in HbA1c and FBS levels in asthmatic children on low dose ICS when compared to controls. Low dose inhaled corticosteroids can be used as the mainstay treatment in asthmatic children without any fear of hyperglycemia.

KEYWORDS

Asthma, Corticosteroids, Children, FBS, Hba1c,

INTRODUCTION

Some common triggers for asthma symptoms like viral respiratory infections and stress are difficult to avoid and should be managed when they occur.[1] ICS are frequently used to treat chronic respiratory conditions such as asthma as they act by reducing inflammation and airway hyper-responsiveness and therefore reduce the risk of exacerbations.[2] Systemic bio-availability of ICS is claimed to be minimal and therefore, the metabolic complications related to ICS use is expected to be negligible. Despite developing various inhalation devices to improve locally targeted delivery of drugs in the airways, significant proportion of ICS can still reach the systemic circulation especially at high doses.

ICS may enter the systemic circulation either through lungs or gastrointestinal tract. It is estimated that, around 10 to 40% of inhaled medications actually make it to the desired location in the airways. The rest is swallowed and reaches gastrointestinal tract,[3] however only a small amount of this actually reaches systemic circulation, since majority of the swallowed dose undergoes first pass metabolism in the liver. In addition, after exerting its desired effect in the airways the ICS eventually gets absorbed systemically resulting in further extra-pulmonary effects.[4]

Systemic effects depend on the type of steroid, the dosage used, pharmacokinetics, type of inhaler, method of administration, and inter-patient differences in susceptibility, response, besides others.[5] As ICS are the recommended treatment modality in asthma, it is imperative that their systemic complications are highlighted and reviewed by the prescribing physician.[6] It is well established that long-term ICS use causes a number of dose-dependent side effects including adrenal suppression, reduction in bone density, ocular hypertension, posterior sub-capsular cataracts and reduction of growth velocity.[7,8] In view of the overwhelming evidence of systemic side effects with ICS therapy, various studies have attempted to explore, its dysglycemic effects and to date there have been mixed results.

ICS have been found to affect the hypothalamo-pituitary-adrenal axis.[9] There have been few case reports acknowledging worsening of the glycemic control in patients commenced on high dose ICS including worsening of HbA1c.[10] Glucocorticoids cause pancreatic β-cell dysfunction, which results in a marked reduction of insulin secretion.[11] The acute and chronic glucocorticoid administration have been shown to reduce β-cell function and insulin secretion in human beings.[12 - 14] HbA1c levels provide an indication of average increase in blood glucose level in asthmatic children using medium to high doses of ICS. This study was an attempt to establish the effect of use of low dose ICS on the glycemic status in children. There is paucity of data regarding, effect of low dose ICS on HbA1c levels and FBS levels in asthmatic children on ICS. So, we took-up this study with an objective to analyze and compare the HbA1c and FBS levels in children with asthma on low dose ICS in non asthmatic children.

MATERIAL and METHODS

A case control study was conducted on children aged between 3 to 14 years, diagnosed as bronchial asthma on low dose ICS for at least 3 months, presenting to pediatric inpatient and outpatient. Children without asthma matched for age and sex presenting to pediatric inpatient and outpatient were grouped as control.

According to GINA 2016 guidelines, Asthma is defined as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

A total of 120 children, who fulfilled the inclusion and exclusion criteria were enrolled in the study and were divided in to study group and control group, each one containing 60 subjects. Study group included asthmatic children, aged between 3 - 14 years, on low dose inhaled CS for a minimum of 3 months. Control group included non-asthmatic children admitted for other problems in the hospital as per the exclusion criteria. 120 children were selected by purposive sampling. Children taking oral steroids, children with diabetes mellitus, children with WALRI, children with acute severe asthma, children with endocrine disorders, co-existent pulmonary, cardiac or renal disease, children who are noncompliant to treatment or use of spacer and children of parents who failed to give consent for the study were excluded. The sample size was calculated based on the expected difference of 0.3 gm% difference of HbA1c levels across 2 groups with pooled standard deviation of 0.58, with alpha of 5% and power of 80%, a sample size of 59 was allotted in each group and was rounded

off to 120 subjects for two groups in our study.

After obtaining informed consent from parents, the demographic information, such as age, gender and the presenting complaints including the family history, history of steroid intake, history of allergies was collected for all cases. Thorough clinical examination was done, and relevant data was entered in a pre-written proforma.

Under aseptic precautions, 5 ml of venous blood was taken by venipuncture in EDTA vacutainer tube and sent to biochemistry lab for HbA1c levels estimation. HbA1c levels were estimated in BIORAD D-10 dual program by High Performance Liquid Chromatography. 3ml of venous blood was taken in a plain vacutainer tube in fasting state and sent to biochemistry lab for FBS measurement. FBS was estimated by GOD/POD (Glucose oxidase/peroxidase) method.

Statistical analysis was done after entering the data collected in to Microsoft EXCEL sheet. Statistical software SPSS version 22 was used for data analysis. Descriptive statistical measures like mean, median, standard deviation and percentages were calculated according to the type of data. Suitable inferential statistics, like Chi-square test and Independent sample-T test were applied, wherever relevant. Data was interpreted, with statistically significant at 'P' value less than 0.05. Graphical presentation was done using Microsoft EXCEL and SPSS version 22.

RESULTS

A total of 120 children were enrolled in the study and were divided in to study group and control group, and each one containing 60 subjects.

Table I - Age distribution of study and control group

AGE GROUP	NUMBER OF SUBJECTS IN CONTROL GROUP	NUMBER OF SUBJECTS IN STUDY GROUP
3-4 YR	4	4
4-5 YR	15	16
5-6 YR	9	11
6-7 YR	5	6
7-8 YR	6	6
8-9 YR	5	3
9-10 YR	2	2
10-11 YR	5	3
11-12 YR	1	2
12-13 YR	3	2
13-14 YR	4	4
14-15 YR	1	1

Maximum children in both study and control group were between 4-6 years. Mean age of the children in the study was 83.27 months and that of control group was 85.10 months.

Gender wise 27 were females and 33 were males in the study group and 28 children were females and 32 were males in the of control group. There was no significant gender difference P value = 0.9. Maximum subjects (30%) used ICS for 4 months duration. Majority (97%) of the subjects in study group have used budesonide as ICS. Only 2 subjects (3%) used fluticasone.

There was a family history of asthma in 16.7% of the asthmatic children.

Table II. Comparison of HbA1C levels between study group and control group

	GROUP			
	CONTROL		ASTHMA	
	Mean	SD	Mean	SD
HbA1C %	5.31	0.29	5.40	0.38

P= 0.2, Independent T test

There was no significant effect of low dose ICS on HbA1c level in the study group.

Mean FBS level between control and study groups, were 84.77 mg/dl and 86.63mg/dl, respectively and the P value was 0.7. There was no significant effect of low dose ICS on FBS level in the study group.

Mean HbA1c level was higher, 5.49 in the group of subjects with family history of asthma (where is this data!) compared to the group with no family history of asthma, 5.33. This was statistically insignificant with a P value of 0.1

Table III. Correlation between duration of ICS, HbA1c and FBS levels

		HbA1C	FBS (mg/dl)
DURATION OF STEROID (Months)	Pearson Correlation	0.218	0.098
	P	0.095	0.456
	N	60	60

There was no significant correlation between duration of ICS and HbA1c levels in study subjects, with a P value of 0.095.

There was no significant correlation between duration of ICS and FBS levels in study subjects with a P value of 0.456 and there was no significant correlation between total cumulative dose of ICS and FBS levels in study subjects and has a P value of 0.807.

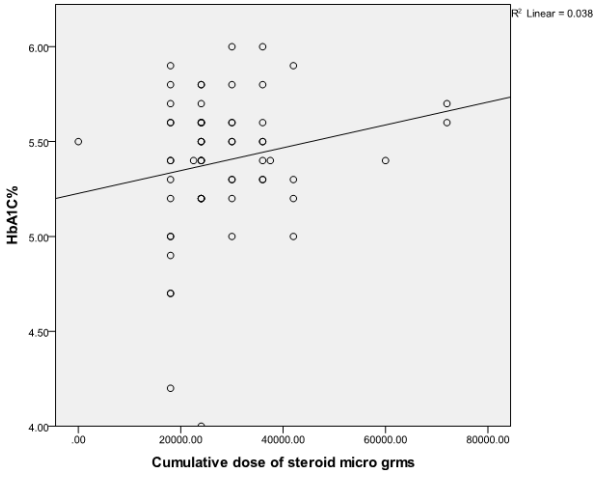

Figure I. Correlation between cumulative total dose of ICS and HbA1c

There was no significant correlation between total cumulative dose of ICS and HbA1c levels in study subjects (P- 0.130).

DISCUSSION

The present study observed that there was no significant correlation between the use of ICS and levels of HbA1c in study subjects with control group (P value of 0.095). There was no significant correlation between the use of ICS and FBS levels in study subjects with a P value of 0.456 and there was no significant correlation between total cumulative dose of ICS and FBS levels in study subjects and has a P value of 0.807. A similar study was conducted by Oya et al at Istanbul, Turkey.[7] They have studied, 141 children in the age group 3 to 12 years, with mild persistent asthma, who were on low dose ICS. The mean HbA1c value was 5.44±0.75% among the children with asthma and 5.14±0.41% in the control group. HbA1c levels in children with asthma was significantly higher than the control group (P=0.006). No significant correlation was found between cumulative dose of ICS and HbA1c levels. Similarly, levels of HbA1c did not change with increased time of usage of ICS (P=0.96).

In contrast, Daniel S et al, have conducted a study on HbA1c profile of 170 asthmatic children between 3 to 12 years, who were on ICS for at least 6 months.[15] HbA1c, FBS, PPBS levels were measured before initiating ICS and after 6 months of ICS, using venous blood samples. There was a significant increase in the mean HbA1c of the total study population, before and after treatment with ICS, and the observation was opposite of that of present study. In the present study, budesonide/fluticasone used was compared to the beclomethasone dipropionate in their study, which may be the reason for higher levels of HbA1c.

Bindusha S et al., have studied children between 1-12 years attending asthma clinic using high dose and low dose inhaled corticosteroids.[16] HbA1c levels, FBS and lipid profile of children in the two groups were measured. There was no statistically significant difference between

the HbA1c levels, FBS and fasting lipid profile, between children on low dose inhaled corticosteroids and high dose inhaled corticosteroids. Alfarttoosi A. J., studied 90 adolescents and adults in the age group 17-48 years, who were on medium to high dose (400-800 mcg/day) inhaled beclomethasone inhaler along with salbutamol therapy.[17] They have compared with the controls who were not on ICS. FBS and HbA1c levels were measured prior to and after 3 months of treatment. Results showed significant increase in FBS and HbA1c in the study group after use of ICS compared to control group.

Lee et al assessed the effects of high dose ICS on cell mediated immunity, using delayed type hypersensitivity skin testing as a measure of impaired cellular immunity.[18] O'Byrne and colleagues, in a retrospective analysis of various clinical trials, failed to demonstrate any increased risk of new onset diabetes or hyperglycemia with the use of ICS in patients with asthma.[19]

The overall benefits and risks associated with ICS use, definitely favors the use in patients with persistent asthma, and all professional bodies agree on this treatment at optimal dosage necessary for proper control of the disease.

CONCLUSION

The present study observed, no significant difference in HbA1c and FBS levels in asthmatic children on low dose ICS when compared to controls. Low dose inhaled corticosteroids can be used as the mainstay treatment in asthmatic children without any fear of hyperglycemia.

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