Section: Paediatrics

Original Research Article

EVALUATION OF BLOOD HBA1C LEVELS IN ASTHMATIC CHILDREN ON LONG TERM (>6 MONTHS) INHALED CORTICOSTEROID

Received : 21/10/2023
Received in revised form : 27/11/2023
Accepted : 09/12/2023

Keywords:
Asthma, ICS, HbA1c, MetS.

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DOI: 10.47009/jamp.2023.5.6.139

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (6); 675-679

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Abstract

Background: The prevalence of asthma in children ranges from 3-38%. Inhaled corticosteroids (ICS) are the most effective controller drugs in the treatment of asthma. Though the adverse effects of systemic corticosteroids have been addressed by the advent of inhalational therapy, reports of alteration in glucose and lipid metabolism particularly on long term ICS are appearing. There are limited studies in the pediatric age group evaluating the levels of HbA1c following use of long-term ICS. The objectives of the present study were to compare the blood HbA1c levels and lipid profile in asthmatic children on ICS for more than 6 months with other asthmatic children on ICS between 1-6 months and to correlate the changes with the dose and duration of ICS. **Materials and Methods:** This was a cross sectional study taken up in Pediatric asthma clinic at Cheluvamba hospital, Mysuru. It was conducted on 56 children aged 1-18 years with asthma (GINA guidelines 2019) on ICS for more than 6 months (cases) and another 56 asthmatic children on ICS for 1-6 months(controls) The comparison of RBS, HbA1c and lipid profile was between the two groups using chi square test and student's t test. **Result:** The mean HbA1c level in cases was 5.43% and 5.27% in controls. The difference was statistically significant (p value=0.34). When lipid profile parameters were analysed, total cholesterol and triglycerides were borderline high in 21.4% of cases(only 1.8% of controls) and 64.3 % of cases(only 44.6% of controls) and difference was statistically significant(p value<0.05). **Conclusion:** Asthmatic children on ICS for more than 6 months had higher values of mean HbA1c, RBS and developed more number of components of metabolic syndrome (like dysglycemia, hypertriglyceridemia, obesity) compared to children on ICS for 1-6 months. Thus children on long term ICS need to be monitored for development of dysglycemia, metabolic syndrome and the associated cardiovascular complications.

INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyper responsiveness triggered by combination of environmental factors and genetic susceptibility.1 According to GINA 2021, Asthma is defined by history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, cough that vary over time and in intensity together with variable expiratory airflow limitation.[1]

Due to spontaneous reversibility of airway obstruction, some children outgrow the disease whereas others develop progressive symptoms and chronic airway modelling which needs treatment. Various non-pharmacological and pharmacologic measures like Beta adrenergic agonists, corticosteroids, anti-leukotrienes, theophylline are used in the treatment of asthma.[2]

Inhaled corticosteroids became the cornerstone of therapy since introduction in the 1980's. Evidence suggests that Inhaled corticosteroids prescription is very effective in childhood Asthma and superior to other drugs used. 2 For the best outcomes, Inhaled Corticosteroids containing treatment should be initiated as soon as possible after diagnosis of Asthma.[3] Inhaled corticosteroids are the most effective controller drugs because of their multiple mechanism of actions including anti-inflammatory, reduction of airway responsiveness, reversal of down regulation and prevention of airway remodeling.3 Benefits are seen within 2-3 weeks of starting therapy.[4]

For safety GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

GINA recommends that all adults and adolescents with asthma should receive Inhaled corticosteroids (ICS) containing controller treatment to reduce the risk of severe asthma exacerbations and to control symptoms.[5]

Although Inhaled Corticosteroids prescription is generally considered safe in children, potential adverse effects related to regular use have been reported and continue to be a matter of concern, with some of them being oral candidiasis, dysphonia and systemic adverse effects like growth delay, adrenal insufficiency and impaired cellular immunity.[6]

Long term use of systemic steroid has been known to cause Hyperglycemia and adverse effect of hyperglycemia is well documented 5 and hence the safety profile of Inhaled corticosteroid is better than systemic steroids. The systemic bioavailability of Inhaled corticosteroids is claimed to be minimal and therefore the metabolic complications related to inhaled corticosteroids 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 inhaled corticosteroid drug molecule.[7]

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.[7,8] Glucocorticoids cause hyperglycemia by increased gluconeogenesis and decreased glucose uptake in the liver and adipocytes by reduced insulin binding.[8]

The HbA1C assay provides an objective, long-term measure of glycemia. There is a strong correlation between HbA1C and blood glucose concentration.[9] Measurement of HbA1C level is useful to assess average blood glucose concentration in previous 8 - 12 weeks and hence its levels can be used for blood glucose monitoring.[10]

MATERIALS AND METHODS

This is a Cross sectional study was conducted in the Cheluvamba hospital, a teaching hospital of Mysore Medical College and research Institute, Mysuru.

Source of Data: Children aged between 1-18 years of age diagnosed as asthma according to GINA 2019 guidelines and have been on regular ICS therapy and attending Cheluvamba hospital Mysuru were included in the study.

Study Design: Inclusion Criteria For Cases And Comparison Group:

Children between 1 year to 18 years of age diagnosed as asthma according to GINA guidelines 20191were enrolled into the study and were allocated into cases (on inhaled corticosteroids for more than 6 months) and comparison group (asthmatic children on inhaled corticosteroids for 1-6 months).

Exclusion criteria for cases and comparison group: Children on oral corticosteroids for more than 14 days in the preceding 4 weeks.

Children with history of co-existing diabetes mellitus.

Individuals with history suggestive of shortened RBC life span which affects HbA1C values like history of acute and chronic blood loss, hemolytic anemia etc.

Method of study:

112 Asthmatic children Diagnosed according to GINA 2019 guidelines and out of which 56 on long term inhaled corticosteroids (>6 months) and 56 asthmatic children on inhaled corticosteroids (1-6 months) were enrolled in the study. All the children were subject to a detailed history and clinical examination including height and weight assessment and detailed systemic examination according to a predesigned proforma. The history included details of Inhaled corticosteroid use like, type of Inhaled corticosteroid, dose, duration, device used for delivery of Inhaled corticosteroids, whether rinsing of mouth done after using Inhaled corticosteroid, compliance etc. Compliance of Inhaled corticosteroid was crosschecked by taking note of number of used canisters as reported by parents, prescription verification and number of doses remaining in the canisters partially used.

RESULTS

[Table 1] shows that most of the cases (66.1%) and controls (82.1%) belonged to the age group of 6 to 11 years. Proportion of children aged > =12 years was higher among cases (32.1%) as compared to controls (3.6%). Proportion of children aged < 6 years was higher among controls (14.3%) as compared to cases (1.8%).

[Table 2] show gender distribution among cases and controls. Approximately, proportion of males is higher among cases than in controls by 10%.

[Table 3] depict Asthma control among the study participants after administration of inhaled corticosteroids. Highest proportion of cases (68%) as well as controls (71%) had their Bronchial Asthma under good control. Asthma in another 27% of the cases and 29% of the controls was partly controlled. Only 5% of the cases and none of the controls had uncontrolled asthma. The difference between the proportions is not statistically significant (p value < 0.05).

Analysis of parameters assessing sugar control are written in table 9. Mean (95% CI) random blood sugar was 142.32 (137.84 – 146.81) mg/dl and 125.71 (121.89 – 129.53) mg/dl respectively. Difference between the two central tendency measures is statistically significant (p value: 0.021). [Table 4]

Also, mean HbA1C was significantly higher among cases (5.43%) than in controls (5.27%) as shown in table 20. However, the mean measures appear to be

ISSN (O): 2687-5365; ISSN (P): 2753-6556

in the normal range. Hence, individual HbA1C values were categorized and later analyzed, summary of which is shared below. [Table 5]

[Table 6] describes status of sugar control among study participants separately for cases and controls. Overall, around 64% cases and 89% controls had well controlled sugar level even after usage of inhaled corticosteroids. The remaining 36% cases and 11% controls were at the stage of Pre-diabetes at the time of the study. The difference between the proportions was found to be statistically significant.

The [Table 7] depict the ICS duration and HbA1C values. It shows that as the duration of ICS use was increased, the percentage of cases showing HbA1C values of pre diabetes proportionately increased. Among the cases using ICS for a duration of 6-12 months around 20.8% had pre diabetic values, those using ICS for a duration of 12-18 months, 26.7% had prediabetic values and those using ICS for more than 18 months, 64.4% had pre diabetic values. The p value computed between the two groups was 0.011, thus there was a statistically significant difference found between ICS duration and HbA1C levels.

[Table 8] depict the distribution of components of metabolic syndrome among the cases and controls. While 28.57% of the cases had any 1 out of the 4 components of the metabolic syndrome, 14.28% had any 2 out of the 4, 7.14% had any 3 out of 4 and 1.78% of the cases had all 4 components of metabolic syndrome. Similarly, in controls, 48.21% had 1 component, 25% had 2, 12.5% had 3 and 5.35% had all the 4 components of metabolic syndrome. The p value between the two groups was not significant.

Table 1: Age distribution among the study participants

Age group	Cases (n = 56)	Controls (n = 56)	Total (n = 112)
< =5 years	1 (1.8 %)	8 (14.3 %)	9 (8.0 %)
6 – 11 years	37 (66.1 %)	46 (82.1 %)	83 (74.1 %)
> =12 years	18 (32.1 %)	2 (3.6 %)	20 (17.9 %)
			112 (100.0 %)

Table 2: Gender distribution among the study participants

Age group	Cases (n = 56)	Controls (n = 56)	Total (n = 112)
Female	21 (37.5 %)	26 (46.4 %)	47 (8.0 %)
Male	35 (62.5 %)	30 (53.6 %)	65 (74.1 %)
			112 (100.0 %)

Table 3: Asthma control among the study participants

Asthma control	Cases (n = 56)	Controls (n = 56)	Total (n = 112)
Well controlled	38 (67.9 %)	40 (71.4 %)	78 (69.6 %)
Partly controlled	15 (26.8 %)	16 (28.6 %)	31 (27.7 %)
Uncontrolled	3 (5.3 %)	0	3 (2.7 %)
	$\chi 2$ statistic: 3.084; p value: 0.214		112 (100.0 %)

Table 4: Comparison of parameters assessing sugar control between the cases and controls

Details about asthma medications	Mean (Standard deviation)		p value (Unpaired samples t-test)
	Cases (n = 56)	Controls (n = 56)	
Random Blood Sugar (mg/Dl)	142.32 (16.79)	125.71 (14.32)	< 0.021*

Table 5: Comparison of HbA1C levels between the cases and controls

	Mean (Standard deviation)		p value (Unpaired samples t-test)
	Cases (n = 56)	Controls (n = 56)	
HbA1C (%)	5.43 (0.3)	5.27 (0.28)	< 0.034*

Table 6: Comparison of sugar control between the cases and controls in terms of HbA1C categories

Sugar control	Cases (n = 56)	Controls (n = 56)	Total (n = 112)
Normal (<5.7%)	36 (64.3 %)	50 (89.3 %)	86 (76.8 %)
Pre-diabetes (5.7%- 6.4%)	20 (35.7 %)	6 (10.7 %)	26 (23.2 %)
Diabetes (>= 6.5%)	0	0	0

Table 7: Distribution of cases according to ICS duration and HbA1C

ICS duration (in months)	HbA1C	
	Normal	Pre DM
6-12	19	5
	79.2%	20.8%
12-18	11	4
	73.3%	26.7%
>18	6	11
	35.3%	64.7%

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 8: Distribution of components of metabolic syndrome among cases and controls.

	Controls	Cases	P value
1 Component	19(28.57%)	27(48.21%)	0.135
2 Component	8(14.28%)	14(25%)	0.153
3 Component	4(7.14%)	7(12.5%)	0.340
4 Component	1(1.78%)	3(5.35%)	0.308

DISCUSSION

The sex ratio in our study showed a male preponderance of 1.66:1, which is consistent with some of the other studies all over the world, except in Wasim et al,[11] where females formed the majority of the study group. Another important consideration in this study was over all male preponderance which is consistent with other studies. The sex ratio is variable across the globe, however there is male preponderance in early childhood. A gender disparity with male predisposition is known in early childhood asthma with a prevalence of 11.9% in boys and 7.5% in girls and boys are also twice as likely as girls to be hospitalized for an asthma exacerbation. However, during adolescence there is decline in asthma prevalence and morbidity in males concurrent with increase in females. By adulthood women have increased prevalence of asthma compared to men.

In the study by Bindusha S et al,[12] 89.2% of study subjects were well controlled compared to 67.9% in the present study. Asthma control is improved by compliance to therapy and a dedicated asthma clinic with trained specialist who advise proper technique of using MDI with spacers, mouth rinsing after use, written asthma action plan being given to the parents of the children in local; language and some children who follow PEFR monitoring. Assessment and monitoring of Asthma has been affected by the severe COVID 19 pandemic and hence could account for increase in number of children who have poorly controlled asthma (5.3%) in our study as compared to previous study conducted by Bindusha S et al (1.2%).

In the present study as well as other studies the mean RBS level was higher in the study group than the control group. In all the other studies, except the present one the p value was not significant indicating that blood glucose alone is not a significant indicator for dysglycenmia. In our study there was a significant difference between the two groups.

In the present study, as well as in other studies the mean HbA1C level in the study group was more than the control group. The difference between the two groups was statistically different as it was in the studies by Masoli et al,[13] and Karthikeyani et al.[14]

In the study by Ashish K et al,[15] though the mean HbA1C level was more in the study group than in the control group, there was no statistical difference. In the studies by Wasim A et al,[11] Daniel S et al,[16] both of which were a prospective follow up study, HbA1C after initiation of 6 months of ICS was more than the levels of HbA1C at the start of study and the difference was statistically different.

In the study by Bindusha et al,[12] the mean HbA1C level was 6.206 ± 1.365% among children using low dose inhaled steroids and 6.013 ± 1.185% among children using high dose inhaled steroids and difference was not statistically significant. The mean duration of inhaled steroid use was 2.621 ± 1.56 years for the children in the low dose ICS group and 1.851 ± 1.245 years for the children in the high dose ICS group. This could explain the higher mean HBA1C values in the low dose ICS group as compared to high dose ICS group.

In the study by Karthikeyani et al,14 8.33% children had HbA1C level in high risk range (5.7-6.4%). However, no child had HbA1C level high enough to be labelled as steroid induced diabetes and the difference was statistically significant. (p-value=0.0067). In the present study, 35.7% of the study group had HbA1C level in pre diabetes range compared to 10.7% in the controls and there was a significant difference between the two groups.

Turpeinen et al. found that serum HDL cholesterol increased significantly by 22% when children were on a dose of 800 mcg/day (medians: 1.18 vs. 1.44 mmol/L) and declined to 1.31 mmol/L when the dose was reduced to 400 mcg/day (Overall P = −0.0319).[17] Yavuz et al. found no significant change of serum fasting triglyceride concentrations (P> 0.05) in 11 asthmatic patients on high dose inhaled steroids.[18] The previous studies have demonstrated an increase in HDL levels in children and adults using inhaled steroids.

In the study by Bindusha et al,[12] there was no statistically significant difference between the lipid profile of the children using low dose inhaled steroids, and high dose inhaled steroids. However, in our study since both the groups were on low dose ICS and the two groups differed with respect to duration of ICS therapy, the cases had a higher mean lipid profile parameters as compared to controls. However, except with respect to total cholesterol where there was a significant difference other parameters showed no significant difference between the groups. When individual lipid profile parameters were categorized and analyzed total cholesterol levels were found to be borderline high in 21.4% of cases and 1.8% controls. Similarly, triglycerides were borderline high in 64.3% cases and 44.6% of controls. The difference in proportions of these two parameters of the lipid profile was statistically significant at p value less than 0.05.

As previously discussed, Metabolic Syndrome is defined by IDF as fulfilling 3/5 criteria including BMI more than 30, hypertension, increased triglycerides, increased HDL and impaired fasting glucose.

Since our study showed higher proportion of cases with elevated triglycerides and higher proportion of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

cases with HbA1C within pre diabetic values, the number of cases and controls with different components of metabolic syndrome was analyzed.

In our study, it was found that 48.21% of cases had 1 component, 25% had 2 components, 12.5% had 3 components while 5.35% had all 4 components of metabolic syndrome. Since data and studies in this field is lacking, further research is needed to study the effect of long-term administration of low dose ICS on the development of metabolic syndrome.

Inhaled GCs are potent anti-inflammatory drugs that have become the mainstay for the treatment of persistent asthma. The CYP3A enzymes are the major P450 enzymes known to metabolize these compounds. Therefore, interpatient variability in the metabolism of inhaled GCs could play a role in steroid resistance and insensitivity. However, the inhaled corticosteroids (ICS) have a better safety profile than the oral steroids. In view of the long term requirement for ICS in childhood asthma, there have been lots of investigations on the adverse effects in the growing children. The major areas of concern have been the local side-effects due to the deposition of the ICS aerosol in the oropharynx and the upper airway, effects due to the absorption of the ICS which may lead to systemic effects on growth, hypothalamus-pituitary-adrenal axis and on various metabolic pathways. The documented effects on the growth are minimal. Similarly, the suppression of the hypothalamus-pituitary-adrenal axis with low doses of ICS is minimal.[19]

CONCLUSION

The mean HbA1C and RBS levels were higher in children on Inhaled Corticosteroids for more than six months compared to children on ICS for less than 6 months. Duration of steroid therapy is an important determent of effect of ICS on HbA1C levels. It was found that 1/5th of cases were in pre diabetic range when using ICS for 6-12 months, ¼th in pre diabetic range when using ICS for 12-18 months and 1/3rd were in the pre diabetic range when using ICS for more than 18 months. The mean total cholesterol and triglyceride levels were higher in children on Inhaled corticosteroids for more than six months compared to children on ICS for less than 6 months. It was found that 1/5th of cases had borderline high cholesterol and 2/3 rd of cases had borderline high triglyceride levels. It was found that ½ of cases had 1 component of metabolic syndrome, ¼ of cases had 2 components, 1/8th had 3 components and around 5% had 4 components of metabolic syndrome.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556