EFFECT OF LONG TERM INHALED CORTICOSTEROIDS ON HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS IN CHILDREN WITH ASTHMA

THESIS

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DECLARATION

I declare that the thesis titled ' Effect of long term inhaled corticosteroids on hypothalamic-pituitary-adrenal axis in children with asthma' embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "Effect of long term inhaled corticosteroids on the hypothalamic-pituitary-adrenal axis in children with asthma" is the bonafide work of Dr. Lekshmi S H carried out under our guidance and supervision in the Department of Pediatrics, All India Institute of medical sciences, Jodhpur.

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DEDICATED TO

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INTRODUCTION

Asthma is the most common chronic respiratory disease in children. It constitutes one of the significant chunks of the patient population in any pediatric OPD and emergency. The term asthma translates into shortness of breath and panting in Greek. It is an entity upon which, for decades, clinicians, pathologists, and pharmacologists have put in so much effort and time in order to device appropriate management. However, it is one of the most under-diagnosed and under-treated conditions worldwide.

Definition of asthma

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. Different authorities have put forward different definitions regarding asthma. According to the latest Global initiative against asthma (GINA) guidelines of 2021, "Asthma 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".

Prevalence of asthma in children

As per the WHO facts sheet of 2019, the estimated global prevalence of asthma is 262 million, and there were around 46100 deaths due to asthma (1). The prevalence of asthma varies from country to country, and for children between the age of 6 -7 years varies from 4 % to 32 % (2).

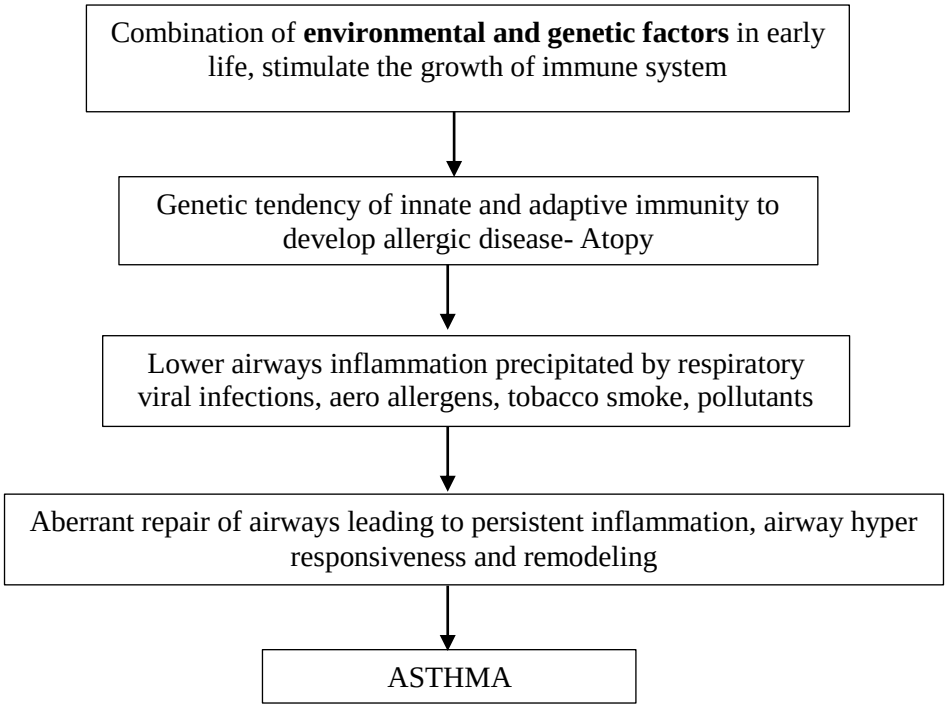
According to a study by Ranbir Pal et al., the prevalence of bronchial asthma in Indian children was 7.24 ± SD 5.42. Childhood asthma among children 6-7 years of age was higher than younger children (13-14 years of age) (2). Prevalence of asthma among school children , assessed with International study of asthma and allergies in childhood (ISAAC) questionnaire(phase 3 study) total prevalence in India was 2.11%in 6-7 year group and 2.84% in 13-14 year group (3). The same study reported the asthma prevalence in various cities of Rajasthan was 2.14% in Jodhpur. In comparison, 5.62% in Jaipur in the age group of 6-7 years and among 13-14 year children, the prevalence was 5.3% in jodhpur, 5.41% in Jaipur, and 7.55 % in Bikaner (3). However' the study done with a similar methodology by our institute reported the

prevalence of asthma among school children of jodhpur aged among age group 6-7 years as 8%, while 9.5% among the age group 13-14 years (4)

Pathogenesis of asthma

The pathogenesis of asthma in children is summarized in Fig-1. Approximately 80 % of all asthmatic patients report disease onset before six years. The significant risk factors of asthma in children include – parent asthma, eczema, inhalant allergen sensitization, and minor including allergic rhinitis, wheezing apart from colds, >4% peripheral blood eosinophils, food allergen sensitization.

Fig-1: Pathogenesis of asthma



The strongest identifiable factor for persistent asthma of childhood is recurrent cough/wheeze with allergy.

Establishing an accurate diagnosis is essential for the appropriate management of asthma. History of variable respiratory symptoms with typical features and confirmed variable expiration flow limitation are the requirements for diagnosing asthma.

Over time, asthma management went through whirlwind changes. If we look into the history briefly, there are documentations of prescribing bizarre agents like the smoke of stramonium (a herb with anticholinergic active ingredients), owls blood with wine(by Aretaeus of Cappadocia, around 100 AD) for the treatment of this condition.

By the 1900s, extensive use of beta-adrenergic agents was being used, initially by using agents like Atropa belladonna. By the 1960 s peak flow inhalers were Invented, and from there, asthma control therapy evolved to its current state. Around the 1950 s anecdotal case reports regarding the use of corticosteroids and ACTH for the treatment of asthma were published, and by 1970 systemic corticosteroids became one of the mainstay therapies for acute exacerbation and prevention. Later on, in view of increased steroid toxicity with continuous use of systemic corticosteroids, inhaled corticosteroids were introduced, and it has been in prevalence since then. (5)

Currently well established and user-friendly guidelines have been put forward by various authorities, and all latest guidelines will be involving ICS as a cornerstone of treatment. Budesonide and Formoterol are now among WHO essential drugs list.

As clinicians, it is essential to have a sound idea regarding the adverse effects of drugs prescribed to our patients for appropriate management, the anticipation of critical outcomes, and to alleviate parents' concerns. As far as inhaled corticosteroids are concerned, the possible side effects include growth retardation, decreased bone mineral density, Hypothalamopituitary-adrenal axis suppression, and secondary adrenal insufficiency. Though extensive research has been done to assess the immediate and long-term side effects of inhaled corticosteroids, clarity regarding ICSs' effect on the HPA axis is not yet gained.

Therefore we planned this study as a humble effort to look into possible adverse effects of ICS, mainly HPA axis suppression.

REVIEW OF LITERATURE

Definition of asthma:

Asthma is a heterogenous disorder characterized by chronic inflammation and hyper airway responsiveness. According to the latest GINA guideline (2021), 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.

Diagnosis of asthma

The diagnosis of asthma in children is mainly clinical and documentation of expiratory airflow limitation in pulmonary function tests (PFT). *History of variable respiratory symptoms with typical features* and confirmed *variable expiratory flow limitation* is the requirement for diagnosing asthma (GINA guidelines).

There are typical clinical patterns for respiratory symptoms in asthma including, wheeze, shortness of breath, cough and/or chest tightness:-

- Patients experience more than one of these types of symptoms.
- Symptoms are often worse at night or in the early morning.
- Symptoms vary over time and in intensity.
- Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

The following are the symptoms that are not in favor of the diagnosis of asthma:-

- Isolated cough with no other respiratory symptoms
- Chronic sputum production
- Chest pain
- Shortness of breath associated with lightheadedness, dizziness, and paraesthesias
- Exercise-induced dyspnea with noisy breathing.

Pulmonary Function Tests

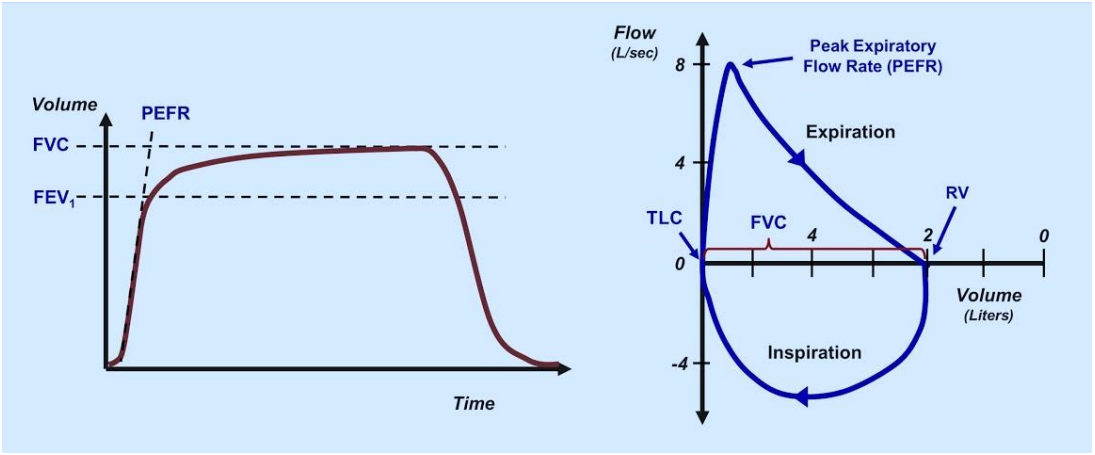
Pulmonary function is assessed with the help of spirometry where, rate of changing lung volumes during forced breathing maneuvers is assessed . It is used to diagnose,

manage, and monitor various respiratory diseases including asthma. It is the cornerstone of the diagnosis and reassessment of asthmatic children.

Children have a dynamic developmental phase during which lung volume size and airway size change with increasing age. Hence, Pulmonary function test parameters are influenced by weight, height, age, sex, environmental factors, ethnicity, prematurity, patient cooperation and effort, and technical factors.

The typical picture of PFT is shown in fig-2

Fig – 2: Typical graphs of spirometry

Flow time graph	**B. Flow volume loop**
	

Expiratory flow limitation in asthma is diagnosed by fulfilling both of the below-given criteria (Table-1):

1. Documented expiration airflow limitation: At a time when FEV1 is reduced, confirm that FEV1/FVC is reduced (it is usually >0.90 in children)
2. Documented excessive variability in lung function (one or more of the following)

Table 1- PFT criteria for the diagnosis of asthma in children

Positive bronchodilator reversibility (BDR) test	• An increase in FEV1 of >12% predicted • **Methods:** Repeat PFT 10–15 minutes after 200–400 mcg salbutamol or equivalent • The drug should be withheld before doing the BDR test:- ▪ SABA ≥4 hours ▪ Twice-daily LABA >24 hours ▪ Once-daily LABA >36 hours
Excessive variability in twice-daily PEF over 2-weeks	An average daily diurnal PEF variability >13%
Positive exercise challenge test	A fall in FEV1 of >12% predicted, or PEF >15
Significant increase in lung function after 4-weeks of anti-inflammatory treatment	Variation in FEV1 of >12% and >200 mL between visits, outside of respiratory infections
Excessive variation in lung function between visits (good specificity but poor sensitivity	Variation in FEV1 of >12% in FEV1 or >15% in PEF between visits

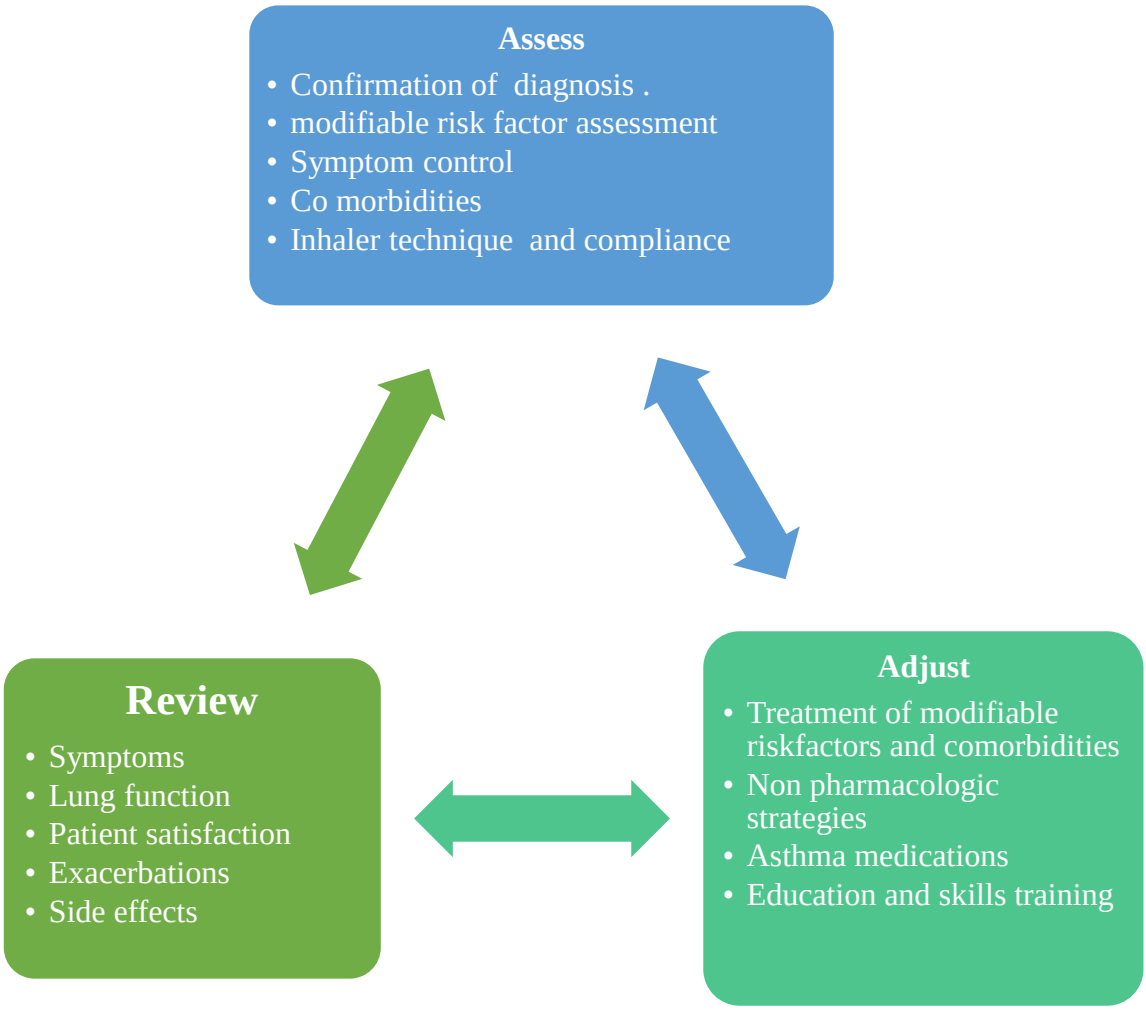
How to interpret lung function test results in asthma

1. A low FEV1 % : Risk of asthma exacerbations is predicted, independent of symptom levels, especially if FEV1 is <60%. It is a risk factor for lung function decline.
2. A 'normal' or near-normal FEV1 in a patient with frequent respiratory symptoms : Consider other causes for the symptoms; e.g., cardiac disease, or cough due to post-nasal drip or gastroesophageal reflux disease
3. Persistent bronchodilator reversibility: Significant bronchodilator reversibility (increase in FEV1 >12% and >200 mL from baseline) in a patient taking controller treatment, or who has taken a short-acting beta2-agonist within 4 hours, or a LABA within 12 hours (or 24 hours for a once-daily LABA), suggests uncontrolled asthma.

Management of asthma in children

*The m*anagement is a continuous cycle of assessment, review, and adjusting the treatment. It has been depicted in figure-3.

Fig – 3: Asthma management cycle



Assessment of Asthma control

Achieving a better control of asthmatic symptoms is essential in preventing acute exacerbations. The extent to which the manifestations of asthma can be observed in the patient or have been reduced or removed by treatment is to be assessed. Symptom control and future risk of adverse outcomes should be looked into. Asthma symptom control should be assessed at every opportunity in evaluation.

Screening tools can be

1. Simple screening tool- GINA symptom control tool, PACS (primary asthma control screening tool, 30 mins asthma test.

2. Categorical symptom control tools: 'Royal College of Physicians (RCP) Three Questions' tool, Asthma APGAR tool
3. Numerical asthma control tool: asthma control questionnaire(ACQ), ACT

Treatment of asthma:

According to the latest GINA guidelines, there are three categories of asthma medications:-

1. **Controller medications:** they contain ICS and will be reducing airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
2. **Reliever medications:** These drugs are to be used in case of breakthrough symptoms including exacerbations.Exercise-induced bronchoconstriction (EIB) can also prevented by these drugs. . Example: as-needed low dose ICS-formoterol or as-needed SABA
3. **Add-on therapies in severe asthma**: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller treatment

As soon as the diagnosis of asthma is made, ICS-containing controller treatment should be initiated , as early initiation of low dose ICS in patients with asthma leads to a more significant improvement in lung function and will be preventing severe exacerbations

After starting the initial treatment, a personalized treatment should be initiated to control and minimize future recurrence of acute exacerbations. It has been summarized in table-2.

Table – 2: Treatment of asthma in children and adolescent

Step of therapy	Symptoms frequency	Preferred controller in 6-11 years of age	Preferred controller in >12 years of age
Step 1	Symptoms less than twice a month	Low dose ICS has taken whenever SABA taken	As needed low dose ICS -Formoterol
Step 2	Symptoms twice a month or more but less than daily	Daily low dose ICS	As needed low dose ICS -Formoterol
Step 3	Symptoms on most days or waking with asthma once a week or more.	Low dose ICS- LABA or Very low dose ICS-Formetrol maintenance and reliever (MART)	Low dose maintenance ICS -Formetrol
Step 4	Symptoms on most days or waking with asthma once a week or more with low lung function	Medium dose ICS-LABA or low dose ICS-Formetrol maintenance and reliever (MART)	Medium dose maintenance ICS-Formetrol
Step 5		Phenotypic assessment with high dose ICS-LABA or add on therapy, anti IgE	Add on LAMA; Consider high dose ICS -Formeterol; anti IgE, anti IL5/5R,anti IL4R

After starting the treatment, personalized management is required for controller medications. The same steps are to be followed as mentioned previously, i.e., review, assess, adjust.

Inhaled corticosteroids

ICS is an unavoidable part of the management of any patient with asthma. Regular use of ICS is associated with decreased frequency of asthma symptoms, bronchial hyperresponsiveness, risk of serious exacerbations, and improved quality of life (6)

Mechanism of action of inhaled corticosteroids

ICS has potent glucocorticoid activity. They reduce inflammation by acting at the cellular level. It decreases the capillary permeability and stabilizes the lysosome at the local site (6). At the cellular level, it inhibits inflammatory genes by reversing histone acetylation via recruitment of Histone deacetylase 2 HDAC2 (7). It has been summarized in table-3. It will also increase the gene transcription of Beta 2 adrenergic receptors, increasing the number of receptors and thus enhancing the effect of Beta 2 agonist reliever therapy.

Table 3 - Cellular effects of inhaled corticosteroids

Increased transcription	Lipocortin -1
	Beta 2 adrenegic receptors
	Secretory leukocyte inhibitory protein
	NF-KB inhibitor
	Anti inflammatory cytokines- IL-10, IL-12, 1L-1 receptor antogonist
Decreased transcription	Inflammatory cytokines- 1L-2, IL-3, IL-4, IL-5, IL-6, IL-11, IL-13, IL-15, TNF α, GM-CSF, SCF
	Chemokines- IL-8, RANTES, MIP-1α, Eotaxin
	Inflammatory enzymes- Inos, COX-2, cPLA2
	Inflammatory peptides- endothelin 1
	Mediator receptors
	Adhesion molecules.

<u>Types of Inhaled corticosteroids</u>

Currently, there are 8 molecular types of ICS available for clinical use

Budesonide/ Budesonide +Formetrol

- Mometasone
- Beclomethasone
- Ciclesonide
- Triamcinolone acetate
- Flunisolide
- Fluticasone propionate

- Fluticasone furoate

Modes of administration

ICS can be delivered through a nebulizer machine, metered-dose inhalers (MDI) with or without spacers, and dry powder inhalers (DPI).

Adverse effects of inhaled corticosteroids

ICS has comparatively lesser side effects than oral corticosteroids. However, prolonged and higher duration of ICS is associated with local and systemic side effects (8). The local side effects of ICs are summarized in Table-4.

Table-4: Local complications of inhaled corticosteroids

Local Complications	
Dysphonia	• Dysphonia due to ICS use is considered to be caused by various causes including myopathy of laryngeal muscles, mucosal irritation, and laryngeal candidiasis (9). • With withdrawal of ICS, dysphonia due to myopathy and mucosal irritation can be reversed. • Incidence is reported from 5 to 58 percent, depending on the patient population, device, dose, length of observation, and manner of data collection (10) (11).
Oral candidiasis	• It is mostly seen among elderly patients and those taking oral corticosteroids/ with any other risk factors. • For patients using MDIs, large volume spacer devices may protect against thrush by reducing the amount of drug deposited in the oropharynx. • In addition, rinsing the mouth and throat with water and expectorating the rinsate after use of all forms of ICS is preventative (9).
Laryngeal candidiasis	• A less common complication of ICS, but has been reported in up to 15 percent of patients complaining of dysphonia during ICS therapy. Isolated laryngeal candidiasis, presenting with dysphonia and sometimes throat pain, has been described in association with ICS in case reports (10)
Oesophageal candidiasis	• Case reports have also described esophageal candidiasis among a few patients using high dose ICS (9)
Contact hypersensitivity	• Budesonide is associated with allergic hypersensitivity in the form of erythematous, eczematoid eruption is typically noted around the mouth, nostrils, or eyes (12)

Systemic side effects

Several factors, including the the site of delivery (i.e., mouth, lungs, gastrointestinal tract), dose delivered to the patient, the delivery system used, individual differences in response to the glucocorticoid, and individual comorbidities (e.g., age, sex , dietary calcium and vitamin D, activity level), influences a patient chance of having systemic side effects

The possible adverse effects of Inhaled corticosteroids include:

1. HPA axis suppression
2. Lung infections like pneumonia,
3. Ocular side effects – glaucoma, cataract
4. Skeletal system – growth deceleration, decreased Bone mineral density

How does ICS cause systemic effects

50 to 90 % of the corticosteroid dose from a MDI is deposited in the mouth or pharynx and is swallowed and absorbed from the gastrointestinal tract (13). However, the "first-pass metabolism" in the liver metabolizes this amount so that only a small amount is absorbed into the systemic circulation (14). Approximately 10 to 40 % of a dose of inhaled corticosteroid is delivered to the respiratory tract. This portion is absorbed from the lung periphery directly into the systemic circulation. Thus, although less of the dose is delivered to the respiratory tract, that is the amount that contributes proportionately more to systemic side effects (15). The budesonide dry powder inhaler (DPI) has approximately 15 to 28 percent lung deposition, while the fluticasone propionate DPI has 20 percent (15) The Dry powder inhalers are supposed to have 60 % oropharyngeal deposition owing to their large particle size, in contrary to pMDIs whch is considered to be around 50 % (16).

It was also found that Systemic effects of ICS may be less detectable in patients with more severe asthma, possibly because airflow limitation inhibits the delivery of drugs to the lung periphery where systemic absorption occurs (17)

Skeletal system: A decrease in bone density, with increase in the use of ICS duration and dosage has been demonstrated in older children by monitoring sensitive markers for bone metabolism (serum alkaline phosphatase, osteocalcin, bone alkaline phosphatase, carboxypropeptide) (18) (19). However, fracture risk does not appear to be increased in children using ICS

A 1041 children (ages 5 to 12) with asthma were randomly assigned to take inhaled budesonide inhaled nedocromil, or placebo for four to six years, in the Childhood Asthma Management Program (CAMP) (20). In the first year, a reduction in growth velocity was noted in the budesonide group, but growth velocities were the same in all groups by the end of the study. The budesonide group had a 1.1 cm lower mean increase in height compared with the placebo at the end of the study.

Skin changes and bruising –topical and oral glucocorticoids can cause easy bruising, skin thinning and telengectasia. Inhibitory effect on dermal fibroblasts leading to loss of extracellular ground substance within the dermis is considered to be the cause for the same. There are reports of increased skin bruising and purpura in patients using high doses of inhaled beclomethasone. However, the degree to which these patients were also receiving intermittent oral glucocorticoids was not described (21). Elderly patients are more associated with easy bruising with ICS is more frequent in elderly patients (22); there are no reports of this problem in children.

Myopathy- There is one case report regarding improvement of muscle weakness with cessation of ICS (23). But Oral Corticosteroids have more stronger association with myopathy.

There are no documented evidence of atrophy of respiratory epithelium (24)or any effect over lipid metabolism (25) with the use of ICS reported.

Hypothalamopituitary axis suppression and adrenal insufficiency

Adrenal insufficiency is of two main types- primary and secondary. Primary adrenal insufficiency is due to disorders that directly affect the cortical adrenal gland, including congenital disorders, autoimmunity, infections like TB, HIV-AIDS, fungal infections – Histoplasmosis, cryptococcosis, coccidioidomycosis, meningococcal sepsis, Trypanososma Brucei, malignancies.

Secondary adrenal insufficiency is due to dysfunction of the anterior pituitary gland or hypothalamus that can cause a deficiency of corticotropin (Adrenocorticotropic hormone [ACTH]), which in turn can lead to adrenocortical hypofunction.

The major etiologies of secondary adrenal insufficiency include abrupt withdrawal of exogenous steroids (systemic and topical), hypothalamic and pituitary tumors, surgery, irradiation, infiltrative processes like hemochromatosis lymphocytic hypophysis , infections like TB, Meningitis, Actinomycosis.

The most common cause of secondary adrenal insufficiency is sudden withdrawal or tapering of a potent glucocorticoid as prolonged administration of high doses of the same agent causes HPA axis suppression. Patients at risk for this problem include those with leukemia, , collagen vascular disease, asthma or other autoimmune conditions and those who have undergone tissue transplants and neurosurgeries.

As far as asthma patients are concerned, the most common situation when secondary adrenal insufficiency occurs is transitioning from oral to inhaled steroids. The maximal duration of glucocorticoids that need to be administered before encountering this problem is unknown, but it is assumed that high dose glucocorticoids that are more than 10 times physiologic cortisol secretion, if administered for more than one week, can precipitate the same condition. (Nelson)

Pathophysiology of adrenal insufficiency in asthmatic patients

The suppression of adrenal glands with ICS use is postulated to be due to the negative feedback exerted by exogenous corticosteroids on the HPA axis. Chronic exposure and/or higher doses can lead to suppression of ACTH production, atrophy of the adrenal glands, and adrenal suppression with subsequent inability to produce a sufficient amount of cortisol. Even after one year of dscontinuation of treatment, this can persist. (26)

The clinical presentation of adrenal suppression is called adrenal insufficiency. It ranges from non-specific and unrecognized symptoms like fatigue, headache, abdominal pain to more concerning manifestations as, hypotension, poor growth, syncope generalized weakness hyponatremia, and hypoglycemia. Those with hypoglycemia, altered mental status, or hypotension should be evaluated urgently for adrenal crisis and treated presumptively with stress glucocorticoids if indicated. It can be asymptomatic also, which may manifest later on.

Although GINA guidelines recommend using ICS, data regarding the systemic side effects of ICS, including HPA axis suppression, is lacking, especially among the Indian population.

There are case reports of children presenting with symptomatic hypoglycemia due to adrenal insufficiency as they were on high dose inhaled corticosteroids(fluticasone) (27)

Considering the possibility of rare but serious side effect of ICS causing adrenal suppression and crisis at the time of stress, various bodies like, Paediatric Endocrine Society Drugs and Therapeutics Committee and the Canadian society of allergy and clinical immunology (CSACI Canada) have put forward guidelines to assess for HPA suppression in children taking ICS especially for longer duration (28)

Assessment of adrenal insufficiency

In general adrenal insufficiency is assessed by two steps if the underlying cause is known (drug/ ICS induced)

1. Establishing inappropriately low S. cortisol measurements,
2. Determining whether this decrease in cortisol levels is independent of ACTH/ Corticotropin stimulation or not

How to assess adrenal insufficiency?

1. ***8 AM cortisol level:*** Cortisol secretion will be maximum during the early morning (6 AM-8 AM) for the normal population, who sleep at night. The normal range is from 10 – 20 mcg/ dl. The interpretation of it has been summarized in table-5.

Table 5 – Serum cortisol levels at 8 am

INTERPRETATION	Cortisol (mcg/dL) (Harriet Lane)
Suggestive of adrenal insufficiency	< 5 mcg/dl
Indeterminate	5-14 mcg/dl
Adrenal sufficiency unlikely	>14 mcg/dL

To assess the utility of serum basal cortisol, to diagnose adrenal insufficiency, it was compared with subnormal cortisol value post insulin induced hypoglycemia. While considering values <5 mcg/dl, specificity was 100% and sensitivity was 36%. When a cut off of 10 mcg/dl was considered, sensitivity to detect adrenal insufficiency increased to 62 %, but specificity reduced to 77 %. Hence low morning serum cortisol concentration alone cannot be used as a reliable indicator to diagnose adrenal insufficiency (29).

In almost all patients, A morning serum cortisol concentration of more than 15 mcg/dL predicts a normal serum cortisol response to insulin-induced hypoglycemia or a short ACTH test (30) ruling out adrenal insufficiency.

2. ***Urinary cortisol levels-*** Basal urinary cortisol levels may decrease in morning samples in patients with adrenal insufficiency. However, it may be low – normal in patients with partial /secondary/central adrenal insufficiency.

Confirmatory tests for adrenal insufficiency

The gold-standard test for confirmation of adrenal insufficiency is the insulin tolerance test, but it has its limitations and contraindications. Metyrapone challenge test and ACTH stimulation tests are other tests to be used to confirm Adrenal insufficiency.

The insulin-induced hypoglycemia test - is used to determine the stress response of the HPA Axis. During this test, baseline blood glucose and cortisol levels, followed by an injection of fast-acting insulin to that measure so that severe hypoglycemia (<40 mg/dl) That is, Neuroglycopenia is induced. In response to stress, ACTH will be produced, and Blood glucose and cortisol levels are measured 30, 45, and 90 minutes after the insulin injection again. The normal response is for blood glucose levels to fall (this represents the stress) and cortisol levels to rise(29).

Metyrapone challenge test is another confirmatory stress test that is easier and less risky than the insulin tolerance test. In this test, metyrapone is administered, decreasing cortisol levels in vivo, thus increasing ACTH production in turn. The immediate precursor of cortisol, 11-deoxycortisol, is also increased. After a single dose of metyrapone overnight,11- deoxycortisol is measured at 8 AM with liquid chromatography (31)

Commonly used confirmatory tests used in clinical practice currently include Short ACTH stimulation tests- Standard dose ACTH stimulation and low dose ACTH stimulation.

Low dose ACTH stimulation test

The low dose (1 mcg as an IV bolus of synthetic corticotropin is injected and S.Cortisol response is assessed after 20 or 30 minutes. A normal response is in the range of 17 to 22.5 mcg/dL , Values less than 17mcg/dl are suggestive of adrenal insufficiency. (32)

Standard dose ACTH stimulation

According to guidelines put forth by the endocrine society, (33) the recommended confirmatory test for diagnosis of adrenal insufficiency is Standard ACTH stimulation test with standard dose (250 μg for adults and children ≥2 y of age, 125 μg for children <2 y of age, 15 μg/kg for infants) IV corticotropin stimulation test. Adrenal insufficiency is indicated by Peak cortisol levels below 18 μg/dL (assay dependent) at 30 or 60 minutes .

Agents use for the test

A commonly used agent, especially in western countries, is Synacthen which chemically is tetracosactide hexaacetate or cosyntropin (34). It is a synthetic form of the peptide hormone corticotropin (ACTH) and has identical 24 residues of N-Terminal of natural corticotropin. It is more potent than ACTH. However, the drug is not easily available in India and hence is expensive.

Hence, ACTH stimulation tests in India are carried out by stimulation with an alternative drug – Acton Prolongatum®. Ferring pharmaceuticals manufacture it. It is a synthetic porcine sequence corticotrophin that is long-acting as it is mixed with carboxymethyl cellulose. Storage of the drug is done at 2-10 degrees C, and it can be administered only via the IM route. In clinical practice, it is used for the treatment of infantile spasms.

Adverse effects – The rare side effects are seen with prolonged use include edema, elevated BP, mood changes, glucose intolerance etc. However, the immediate side effects post one-time administration is not known.

The original article titled IM ACTH stimulation for assessment of adrenal function by authors Abhay Gundgurthi, MK Garg, MK Dutta, validated the usefulness of Acton Prolongatum® as intramuscular ACTH stimulation test (35). In the test , they injected 250 mcg (25U) of Acton Prolongatum® via IM route, and serum cortisol was

assessed after 60 minutes. It was found that all patients with known Adrenal insufficiency had basal cortisol <3 mcg/dL and subnormal response (<18mcg/dL) to ACTH stimulation. They concluded that basal cortisol level less than 3 mcg/dL had 100% specificity in diagnosing AI, but poor sensitivity of 60% (PPV – 100%, NPV – 77.6 %) and that IM ACTH stimulation with the easily available and less expensive drug Acton prolongatum is feasible.

A similar study was done and published in 2019 by the endocrinology department of Government medical college Trivandrum (36). They compared the Syntacthen stress test with APST on the same subjects. It was found that serum cortisol cut-off of 19.5 mcg/dL at 120 min following stimulation with Acton Prolongatum® showed a sensitivity of 100% and specificity of 88 % and concluded that APST could be used to diagnose glucocorticoid insufficiency accurately.

We did a literature search for effect of ICS in children with asthma. Table-6 summarizes the effect of ICS in children with asthma.

Table 6 – Summary of related studies in literature

Author	Year, place	Title	Sample size, Age group	Method	Outcome measure
KWDA A et al.	2019, Srilanka	Effect of long term inhaled corticosteroid therapy on adrenal suppression, growth and bone health in children with asthma (37)	140 (70 cases, 70 controls 3-9 years	Low dose IV ACTH was injected and after 30 minutes, serum cortisol was analysed. In children between ages 3 to 9 . Children with < 500 nmol/L of peak cortisol levels,30 min after the LDAT, was considered to have adrenal suppression	17 children (24.3%) of the study population had a suppressive effect on HPA axis 13 (76.5%) of the 17 patients in whom adrenal suppression was documented used ICS for >24 months
Ozlem Cavkaytar et al. European journal of pediatrics	2015, turkey	Evidence of hypothalamic-pituitary-adrenal axis suppression during moderate-to-high-dose inhaled corticosteroid use (38)	91; up to 18 years	Moderate dose-176 mcg High dose- >264mcg Those with 8 am s. cortisol <15 had low dose ACTH stimulation test(LDAT) to diagnose HPA-axis suppression	60 patients out of total 91 underwent LDAT. 7.7% children of the total population was found to have HPA axis suppression Children taking both High and moderate dosee included among those with HPA suppression. at least 7 months of moderate or high dose ICS use was seen in patients with axis suppression from those with normal axis

Smith RW et al. Pediatric and child health	2012	Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid (39)	214; 8months- 18 year olds	Morning serum cortisol levels and low-dose adrenocorticotropic hormone stimulation testing.	9.3%, of the study population had HPA axis suppression. Increasing dose of ICS use was associated with increased odds of HPA axis suppression. Lower or medium dose of iICS was used by all children with HPA suppression.
Choi IS, et al. Annals of allergy, asthma, immunology	2017	Adrenal insufficiency associated with long-term use of inhaled steroid in asthma (40)	121 Adults with minimum 6 months ICS treatment.	All underwent standard ACTH stimulation test. AI was defined as a morning serum cortisol level no higher than 3 μg/dL or lower than 18 μg/dL before and after administration of 250 μg of ACTH.	With the increasing cumulative dose of ICS , number of subjects affected with HPA axis suppression also increased. patients with asthma might have AI even with low- to medium-dose ICS treatment when ICSs are administered over a long period
Dorsey et al	2006	Assessment of adrenal suppression in children with asthma treated with inhaled corticosteroids : use of dehydroepiandrosterone sulfate as screening test (41)	59 children	Low dose(max 1mcg)IV cosyntroppin test followed by standard dose (250 mcg IV cosyntroppin stimulation and assessment of serum cortisol values.	13(59%) of study population had abnormal response(<18mcg/dl)of cortisol post ACTH stimulation.

Skoner DP, et al	2011	Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma (42)	187; 4-9 years	Children were randomized to MF-DPI 100 μg once daily in the morning , 100 μg twice daily (BID), 200 μg OD, or placebo for 52 weeks followed by a 3-month follow-up period. The primary outcome was growth velocity calculated from heights recorded at each visit. Secondary outcomes- serum and 12-h urinary cortisol, serum osteocalcin, and urinary N-telopeptide.	change in mean growth velocity with MF-DPI 200 μg OD reached statistical significance (-0.70 ± 0.29 cm/y, p = 0.02). The effects of all examined doses of MF-DPI on mean plasma cortisol levels were similar to cortisol changes seen in the placebo group, suggesting an absence of drug-related effects. No differences in 12-h urinary cortisol or other outcomes were observed between groups.
Eid N et al PEDIATRIC DRUGS	2002	Decreased morning serum cortisol levels in children with asthma treated with inhaled fluticasone propionate (43)	62	observational long-term study, Morning cortisol levels were monitored after patients had been on fluticasone for a mean of 8.0 +/- 5.2 months.	Twenty-two patients (36%) had abnormal morning cortisol levels while on fluticasone 17 % of children with low dose ICS and 43 % of children with high dose ICS had abnormal values.

Skoner DP, BergerWE, et al Pediatrics February	2015	Intranasal triamcinolone and growth velocity.(in perennial allergic rhinitis) (44)	1068	randomized, double-blind, placebo-controlled, parallel-group, multicenter study. effect of TAA on the growth velocity (GV) of children aged 3-9 years with PAR by using stadiometry at baseline (4-6 months), during treatment (12 months), and at follow-up Hypothalamus-pituitary-adrenal (HPA) axis function was assessed by measuring urinary cortisol levels	No HPA axis suppression was detected a small, statistically significant effect of TAA-AQ on the GV was detected.
Brian J Lipworth	1999	Systemic adverse effects of iNhaled corticosteroid therapy (45)	Meta analysis and systematic review (27 studies)	Marked adrenal suppression wiith the use of high doses of ICS –>1.5 mg/day (>0.75mg/day of Fluticasone propionate) Fluticasone had greater potency of sdrenal suppression compared to budesonide, beclomethasone, triamcinolone	

A systematic review done by Zollner EW (46) in 2007 considered randomized-controlled trials, cohort, and case-control studies designed to detect HPA suppression caused by ICS, with the help of Insulin tolerance test or the metyrapone test, performed on asthmatics of all ages not on oral steroids. Only four out of the total 22 studies met the criteria for inclusion. All of these were published before 1988. It assessed the HPA suppressive effects of being fluticasone propionate and budesonide given via CFC MDI without spacers. It concluded that reliable data regarding HPA axis suppression by ICS is lacking. The study by Vaz et al. reported that the baseline risk for HPA suppression is 0%. In comparison, the absolute risk is 100% in asthmatic children treated with a beclomethasone dipropionate MDI at a dose of 250– 600 micrograms /m2/day for 6–42 months.

The Srilankan study, by ANURADHA KWDA et al. (37) case-control study done in 2019, studied 70 children with asthma on long-term ICS (more than six months) and 70 controls. Low dose IV ACTH was injected, and after 30 minutes, serum cortisol was analyzed. The study population included children between ages 3 to 9. Children with a peak cortisol level of < 500 nmol/L 30 min after the low dose adreno-corticotropin test were considered to have adrenal suppression. HPA suppression was seen in 17 children (24.3%) of the study population. ICS had been used for more than 24 months in 13 (76.5%) of the 17 patients in whom adrenal suppression was documented. There was a statistically significant association between ICS duration and HPA axis suppression ($\chi 2$ = 12.291; df=3; p<0.01). High doses of ICS (>400 mcg/day) was received by ten (58.8%) of the total 17 children with HPA axis suppression.. The association between adrenal suppression and dose of ICS use was also statistically significant ($\chi 2$ = 29.80; df = 2; p < 0.01).

The retrospective analysis done in Turkey by O. Cavkaytar (38) in 2015 studied The HPA axis status of patients who were on moderate-to-high-dose ICS [>176 and >264 µg/ day fluticasone propionate-hydrofluoroalkane (FP-HFA) for patients,12 years and more than 12 years respectively). Children who had 80-90 percent compliance to ICS and who were taking it for a minimum of 6 weeks were included in the study. Fluticasone propionate , budesonide, and ciclesonide were studied. First, patients were screened for baseline serum cortisol levels with fasting 8 AM samples. In children with baseline cortisol levels less than 15mcg/dL, Low dose ACTH stimulation test

(LDAT) was performed with an IV injection of 0.5 mcg/m2 of synacthen. A 31 children had basal cortisol levels of more than 15 mcg/dL. More than 19.5 mcg/dL serum cortisol post ACTH stimulation in serial blood samples withdrawn at 30 mins and 60 mins indicated a normal HPA axis. Total 91 patients were enrolled in the retrospective study, of which the majority (74.7%) was taking fluticasone propionate, 17% was taking budesonide, and 7 % was taking ciclesonide. 60 patients (75.9 %) underwent LDAT, and seven (7.7 % of the study population, 95 % CI 3.5–15.3 %) were diagnosed with HPA, post LDAT serum cortisol less than 19. Among those with HPA axis suppression, 42.9% were taking fluticasone propionate,42.9% were taking ciclesonide, and 14.3% were taking budesonide.

The study by Smith et al. (39) in 2012 also tried to look into the prevalence of HPA axis suppression in children with asthma. Any children of the age 8 months to 18 years who are on inhaled and intranasal corticosteroids were included. After assessing the presence of any clinical features of HPA axis suppression, 8 AM fasting cortisol levels of the children were assessed. With the cut-off of 170 nmol/L(6.16 microg/dL)children were made to undergo IV LDAT with synacthen >500nmol/L (> 18 microg/dL) was considered to be normal. Of the total study population of 214 subjects, 43 children (20%) had lower values of baseline serum cortisol, making them eligible for inpatient LDAT. A total of 20 children (9.3%) had confirmed HPA axis suppression which was 46.5% of those with low morning serum cortisol levels. Medium or lower dose of ICS for their age was used by all children with HPA axis suppression.. None of the children with HPA axis suppression used Budesonide ICS; however, only 2 percent of the children with normal HPA axis were using the same. The research team put forward that in addition to the proposal to screen children with a high dose of ICS (>500mcg/ day of fluticasone) or equivalent by US guidelines and European guidelines (>400mcg/day of fluticasone or equivalent), children on medium-dose should also be screened for HPA axis suppression.

A similar case-control study in the adult population by Choi et al. (40) from Korea was done in 2017 to assess the HPA axis among adults on long-term ICS. The data of 121 adults who were taking ICS for a minimum duration of 6 months, attending OPD, who received less than two times oral corticosteroids in the past 6 months were included in the study. 8 am cortisol was assessed, followed by ACTH stimulation with 250 mcg of synthetic ACTH (synacthen)administered IV and S. cortisol estimation at

60 minutes. Less than three mcg/dL of 8 am cortisol or Post ACTH stimulation cortisol value less than 18 mcg/ dL was considered Adrenal insufficiency. None of the subjects had less than 3 mcg/dL of S cortisol level among the control group, but 2 had abnormal response post ACTH stimulation. The mean cumulative use of ICS in the study was 3.8 years. Among the low- to medium-dose ICS users for a relatively short period (short-term users) there was 44% prevalence of HPA axis suppression. ; and 61.0% of the long-term (mean duration 11.5 years) low- to medium-dose users showed AI.

RESEARCH QUESTION

- Can long-term use of inhaled corticosteroids cause Hypothalamo- pituitary axis suppression in children with asthma?

AIMS AND OBJECTIVES

Primary objective

- Effect of long-term (>6 months) ICS on the HPA axis in children with asthma.

Secondary Objective

- To assess the effect of long-term ICS use on:-
    - Growth (height, weight, BMI)
    - Blood pressure
    - Skin changes (easy bruising, skin thinning), voice, oral candidiasis

WHAT IS ALREADY KNOWN ON THIS SUBJECT?

1) Prolonged Use of ICS irrespective of dose (low, moderate, and high doses) may suppress the HPA axis.
2) There is some evidence regarding the effect of long-term ICS use on children's growth.

LACUNAE IN EXISTING KNOWLEDGE

1. There is a paucity of studies on the effect of ICS on the HPA axis in children, especially from developing countries like India.
2. There is a paucity of studies on prolonged use of ICS on child growth, especially from developing countries like India.

MATERIALS AND METHODS

Study design: Cross-sectional study

Study setting: Paediatrics OPD AIIMS Jodhpur

Inclusion criteria:

- Children (5-18 years) diagnosed with asthma as per GINA guideline, on long-term treatment with ICS for a minimum of 6 months.
- Parents or guardians had given informed written consent for the enrollment of the child.

Exclusion criteria:

- Children having an exacerbation of asthma or h/o intake of any oral corticosteroids within the past 4 weeks
- Children with any recent h/o surgeries or any systemic infection
- Children with any diagnosed endocrinological (hypothyroidism/ hyperthyroidism/diabetes mellitus) disease

Data collection:

The sample collection was started soon after the first wave of the COVID pandemic in India. Telephonically all children registered in the pediatric Chest clinic were screened to check whether they met inclusion criteria. The duration and compliance of ICS were assessed. If they find eligible, children were called to attend physical OPD.

All the children attending the physical OPD were thoroughly evaluated, and details regarding demographics, age of diagnosis of asthma, duration of ICS, compliance to ICS, asthma control assessed with ACQ questionnaire, use of Oral corticosteroids in past 4-weeks, use of reliever medications in past 4-weeks, the technique of ICS intake, any symptoms suggestive of adrenal insufficiency, anthropometric parameters (at the time of visits and at the first visit,) including height, weight and BMI, Blood pressure, and general examination to look for any physical evidence of complications of corticosteroid use. Children were reviewed, and consent was taken from one parent before enrolling in the study.

Assessment of Asthma control

Asthma control was assessed with GINA asthma control assessment and ACQ scoring in our study among all subjects.

GINA asthma control questionnaire included four questions based on one week recall:-

1. Daytime asthma symptoms more than twice a week
2. Any night awakening due to asthma
3. Reliever needed for symptoms more than twice a week
4. Any activity limitation due to asthma

The presence or absence of the symptoms mentioned above are assessed, and if present, one point is given. A total score of 3-4 is considered poorly controlled asthma, while a score of 1-2 is partly controlled asthma. If the child does not have any of the symptoms mentioned above, it is considered well-controlled asthma.

Asthma control questionnaire (ACQ)

It is also a simple questionnaire containing seven items based on one-week recall. The score for each item ranges from 0 to 6, with 0= no impairment and 6= maximum impairment for symptoms and rescue use. The average of the total score for the seven items is taken. A score of <0.75 is categorized into well-controlled asthma , 0.75 – 1.5 is partly controlled asthma, and >1.5 is poorly controlled asthma. For this study, we have taken partly and poorly controlled asthma together.

Screening with 8 AM fasting serum cortisol levels

Initially, screening for adrenal insufficiency was assessed with fasting 8 AM cortisol levels; for that 2 ml venous blood sample was taken.

Serum cortisol levels were assessed in the institute's Biochemistry lab with a chemiluminescence kit based on the SPALT principle (Solid-phase antigen linked technique) with a Liaison® analyzer. The intra-assay and inter-assay coefficient of variation was below or equal to 5.3% and 9.3%, respectively.

Serum cortisol level cut-off was kept at 15 mcg/dL. All children with cortisol levels less than the cut-off were called back again for the confirmatory test with standard ACTH stimulation on an OPD basis. All children with 8 AM fasting cortisol levels more than or equal to 15mcg/dl were considered to have a normal HPA axis.

Standard dose ACTH stimulation

The usual practice of the Standard ACTH stimulation test with synacthen was not feasible in our setting due to the nonavailability and price of the drug. Hence modified ACTH stimulation with IM Acton Prolongatum ® was used. In this test, 25 Units of IM Acton Prolongatum® (4 ml) was injected and serum cortisol levels were assessed after 60 minutes. Post administration, children were observed for one hour to look for any adverse reactions.

Interpretation of ACTH stimulation test:

All children who had serum cortisol levels less than 18 mcg/dL post-ACTH stimulation test were labeled to have adrenal insufficiency. Serum cortisol value ≥ 18 mcg/dl) was considered to have not HPA axis suppression.

Sample size

Based on the previous study (38)**,** we assumed 5% of asthmatic children in our setting might have HPA axis suppression. With 5 % precision and 95 % confidence interval, the calculated sample size is **73**.

STATISTICAL ANALYSIS

- Statistical analysis was performed with SPSS 23.
- The categorical and continuous variables were expressed as frequency (percentage) and median and interquartile range as appropriate (The values did not have normal distribution)
- Descriptive statistics were used to summarise demographics, medical history, compliance, a technique of ICS use, age of diagnosis of asthma, any complications due to ICS use, asthma control etc.
- Association between two or more qualitative variables was assessed using chi-square test.
- Quantitative data between two variables between independent groups were assessed using the Wilcoxon Rank sum test and the Kruskal Wallis test among > 2 groups.
- P value < 0.05 was considered statitical significant.

Ethics and dissemination:

- **Research ethics approval**: The study was undertaken after the ethical clearance from the institute`s ethical committee.
- **Consent:** Informed consent was obtained from parents or guardians before enrolling in a study. The purpose and design of the study were explained to the child's parents.
- **Confidentiality:** The confidentiality of information obtained was maintained

OBSERVATION AND RESULTS

A total of 270 children were screened telephonically as well as physically during the period of study, and 110 children were found to be eligible to be enrolled in the study. However, only 89 children turned up in physical OPD, and only 81 gave consent to be enrolled in the study. The flow study is shown in **Fig-4**.

Fig 4: Diagram showing flow of study

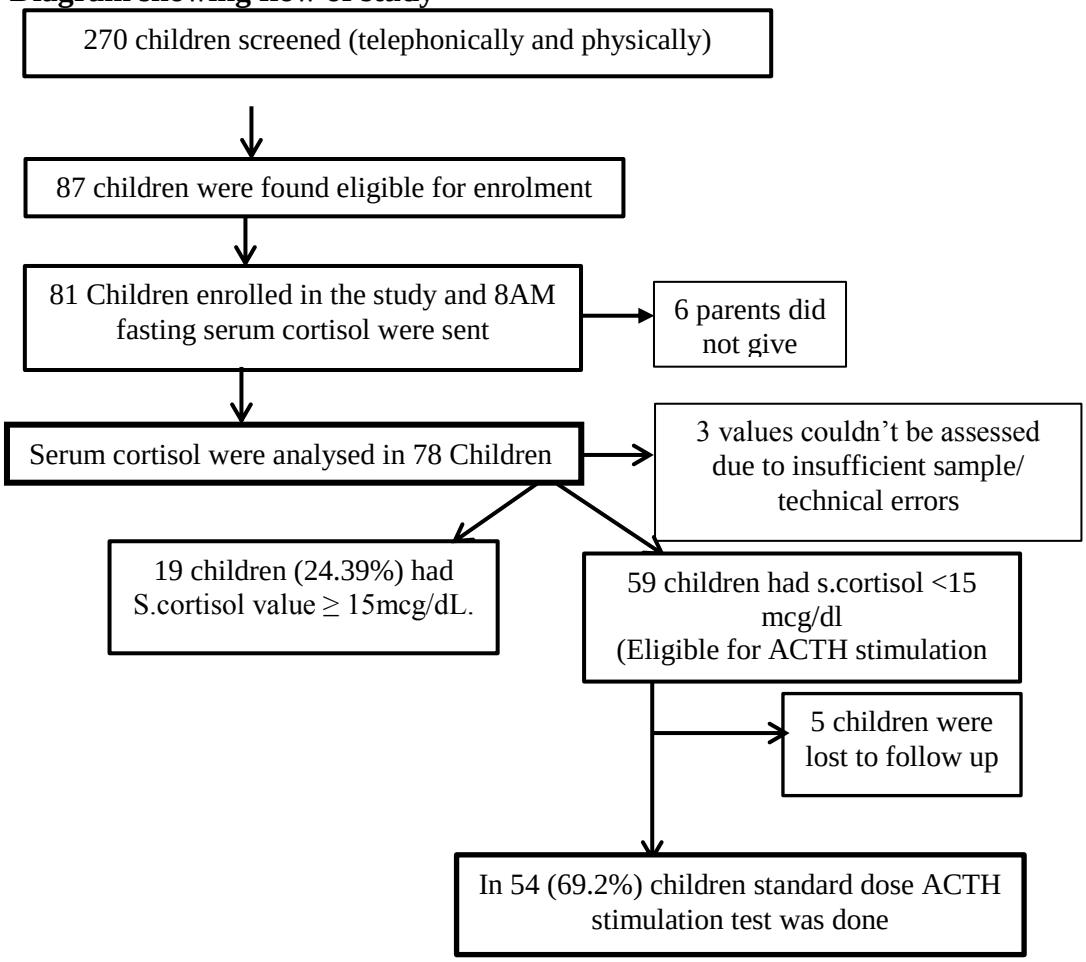


Fig-4: Flow of the study

Baseline characteristics:

The baseline characteristics of enrolled children have been summarized in Table-7.

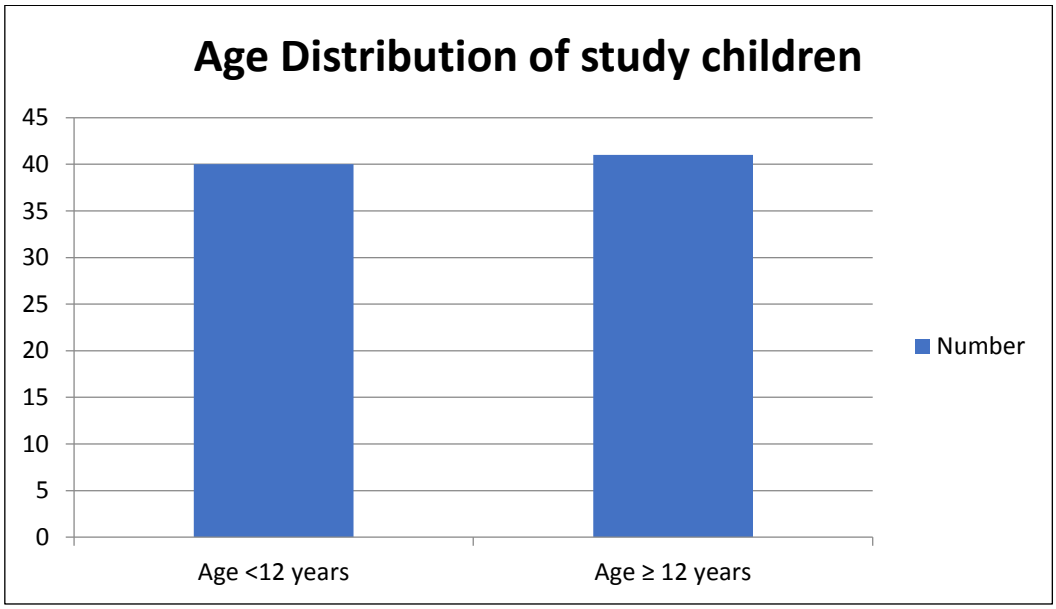
Table-7: Demographic Characterises of Enrolled Children (n=78)

Characterises	Number (%)
Gender	
Male	55 (70.5)
Female	23 (29.5)
Residence	
Urban	40(50.6)
Rural	38(49.4)
Anthropometry at **first-visit**, (Z score), Median (IQR)	
Weight	-0.165(-0.98,0.76)
Height	0.315(-0.54,1.05)
BMI	-0.027(-0.041,-0.017)
Anthropometry at **enrolment**, (Z score), Median (IQR)	
Weight	-0.13(-1.03,0.84)
Height	0.39(-0.64,1.23)
BMI	-0.37(-1.21,0.55)

Age of children

The study population had a median (IQR) age of 11.5 (8, 14) years. Of them, 40 children were younger than 12 years, and 41 children were≥12 years.

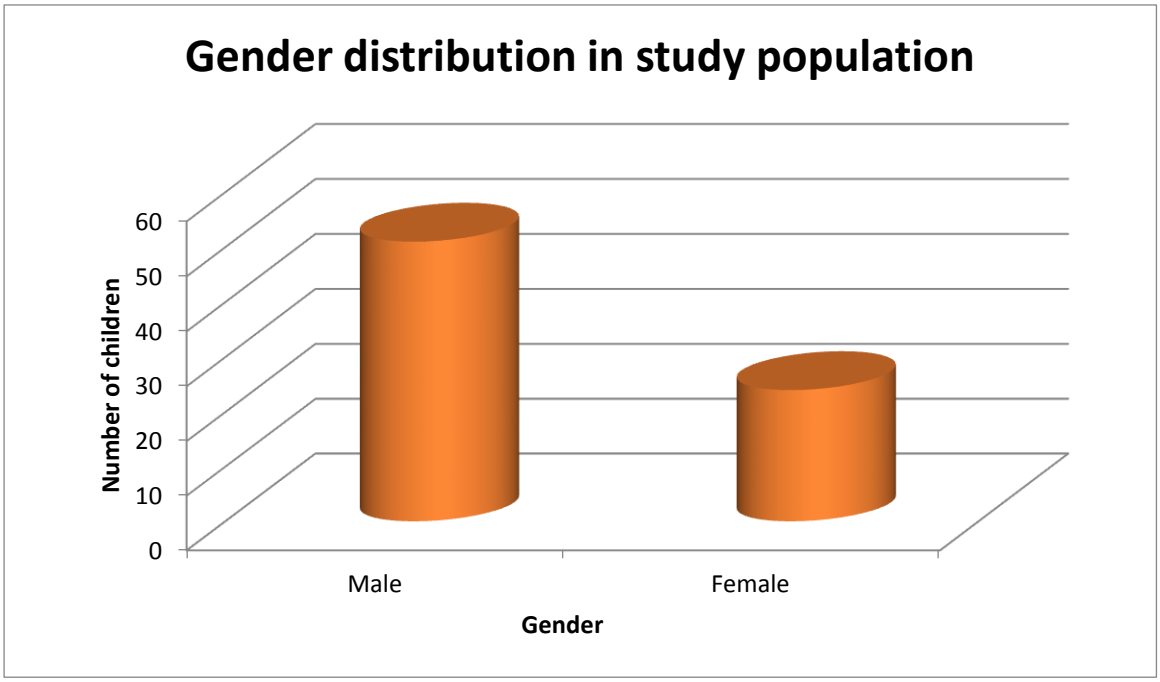
Fig-5: Age distribution of study children(n=78)



Gender

A 55(70.5%) were male children in the study population, and female children were 23 (29.5%).

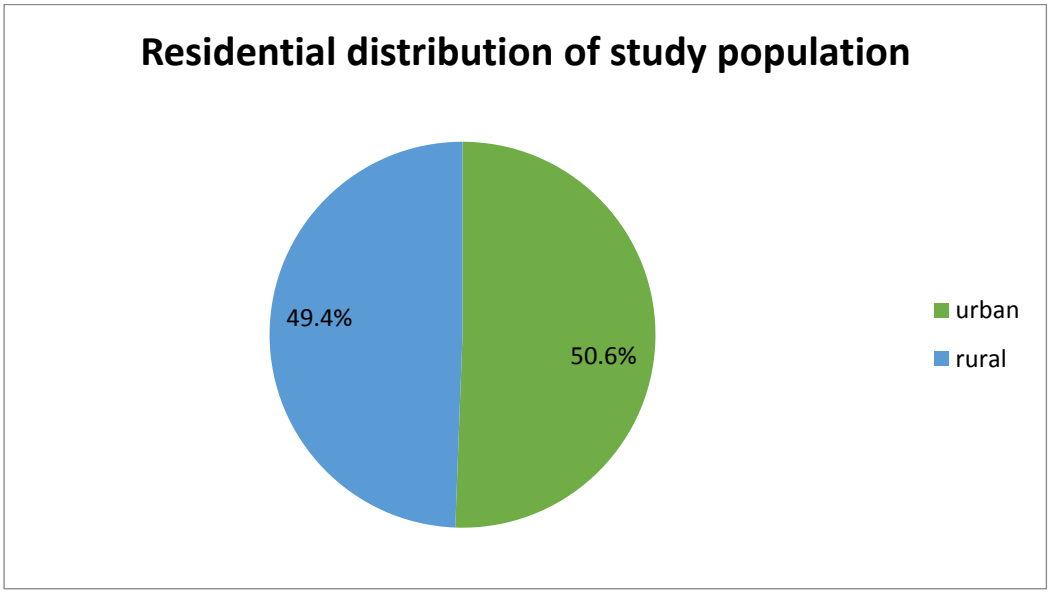
Fig-6: Gender distribution in the study population



Residence:

50.6 % of children were from urban residences, and 49.4% were from rural residences. It has been shown in Fig-7

Fig 7: Residential distribution of study population



Anthropometry

At first visit: The median (IQR) height at the first visit of the enrolled children was 132.5 (116, 145) cm, while Z score had a median (IQR) of 0.315(-0.54, 1.05). The median (IQR) weight at the first visit was 26.1 (19.5, 38.3) kg, and Z score had a median (IQR) of -0.165 (-0.98, 0.78) whereas Z score of BMI among the study population was -0.03(-0.04, -0.02)

At enrolment: The median height at the time of enrolment was 140 (126.5, 153.5) cm, while the Z score median was 0.39(-0.64,1.23). The median weight at the enrolment was 35(24, 45) kg, and the Z score had a median of -0.13(-1.03,0.84), whereas the Z score of BMI had a median (IQR) of -0.37 (-1.24,0.55).

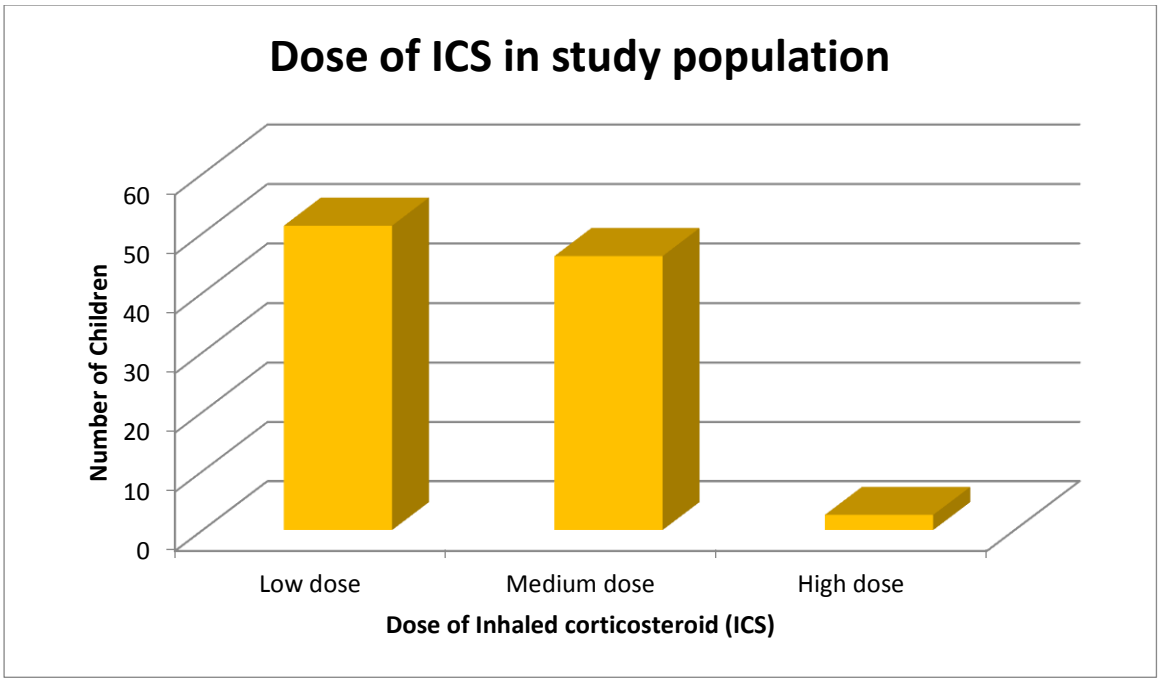
Asthma related characteristics in enrolled children

Asthma-related characterizes of enrolled children are summarized in table-8

Age of onset: The median (IQR) age of diagnosis of asthma of the study population was 6 (5, 9) years.

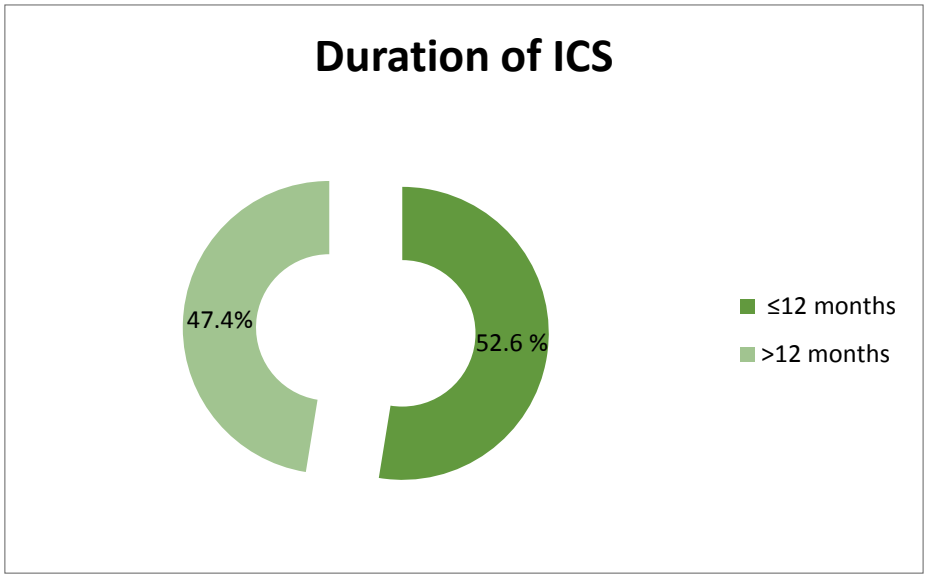
Dosage of ICS: In the study population, 40 children (51.28%) were taking low dose ICS (100 - 200 mcg/day), 36 children (46.15%) on moderate dose (> 200 – 400 mcg/day), and 2 children (2.56%) were taking high dose (> 400mcg/day) ICS.

Fig- 8: Dosage of ICS among study population (n=78)



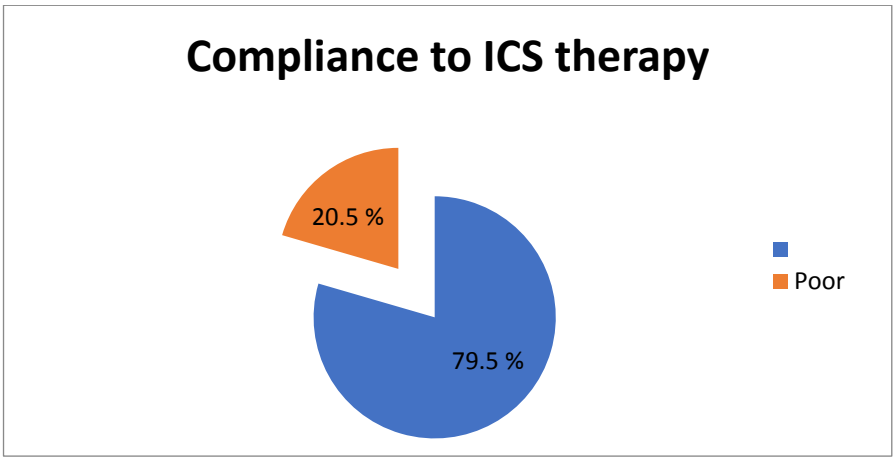
Duration of ICS use: The median (IQR) duration of ICS intake was 12 (12, 24) months. The number of children taking ICS for ≤ 12 months was 41(52.56%), and 37 (47.44%) children were taking ICS for > 12 months. It is represented in **Fig-9**

Fig -9 : Duration of ICS in study population (n=78)



Compliance: There was good compliance to ICS among 62(79.5%) children, while 16 (20.5%) children were poorly compliant to ICS. It is represented in **Fig-10**.

Fig-10: Compliance to therapy among study population (n=78)



The technique of ICS use: The use of the spacer with ICS was followed by 76 children (97.44%), and 2 (2.56%) were not using a spacer. The habit of rinsing of mouth post ICS was observed in 52 children (66.6%), and 26 children (33.3%) did not rinse their mouth after ICS.

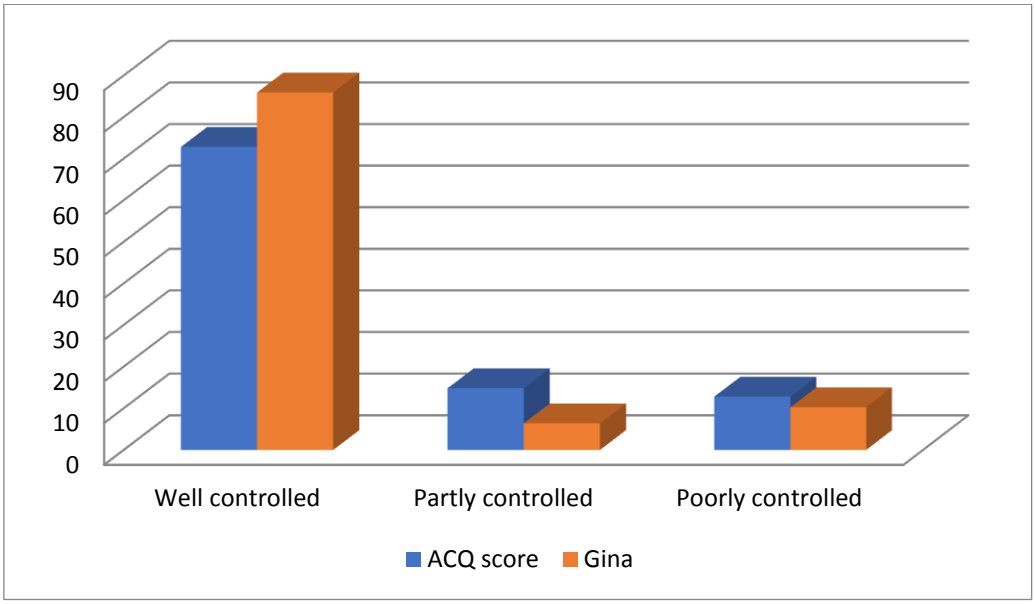
Table-8: Asthma-related Characteristics of Enrolled Children (n=78)

Characteristics	Median (IQR)
Age at diagnosis	6 (5,9) years
Duration of ICS	12(12,24) months
Dose of ICS(n, %) 100-200mcg/day >200-400mcg/day >400mcg/day	 41(52.55) 35(44.87) 2(2.56)
Compliance to therapy Good Poor	 65(83.3) 13(1.6)
Spacer use (n, %) Used Not used	 76 (97.4) 2(2.6)
Mouth rinsing after ICS use, (n,%) Present Absent	 52(66.6) 26 (33.3)

Assessment of asthma control

Asthma control among the study population was assessed with an ACQ score and GINA score. According to ACQ scoring, 56 children (72.15 %) had well-controlled (ACQ score<0.75) asthma while 12 (15.2%) and 10 (12.6%) children had partly controlled(ACQ 0.75 – 1.5) and poorly controlled (ACQ >1.5) asthma . However, with GINA scoring 65(85.9%), 5(6.4%) and 8(10.25%) children had well-controlled, partly controlled, and poorly controlled asthma, respectively. Being an objective test, in our study, further analysis was performed with ACQ scoring.

Fig-11: Asthma control in study population (n=78)

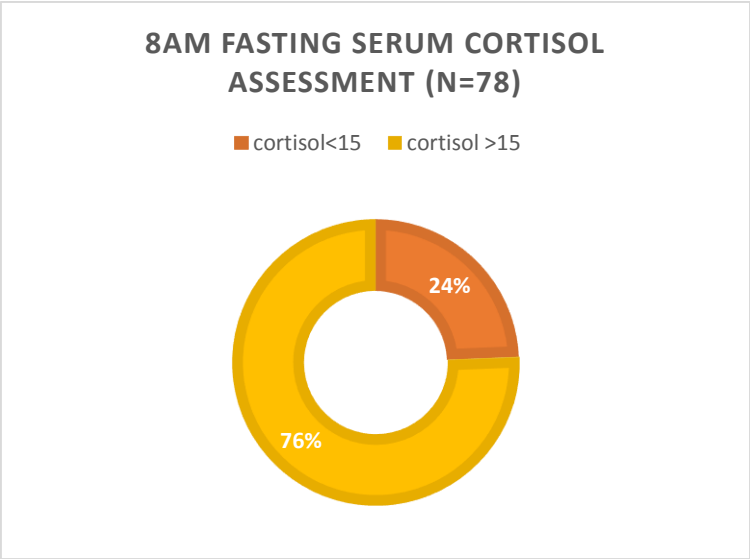


Primary Objective: The primary objective of our study was to assess the effect of long-term (> 6months) ICS use on the hypothalamic-pituitary axis. We analyzed the association of serum cortisol level (baseline and stimulated) with ICS duration and dosage for this objective.

8 AM fasting serum cortisol level in study subjects

The median (IQR) serum cortisol level in enrolled subjects was 8.32 (5.25, 15.2) mcg/dl. Out of them, 19(24.3%) children had value ≥ 15 mcg/dl, while 59 (75.6%) children had cortisol level < 15 mcg/dl. It is represented in Figure 12.

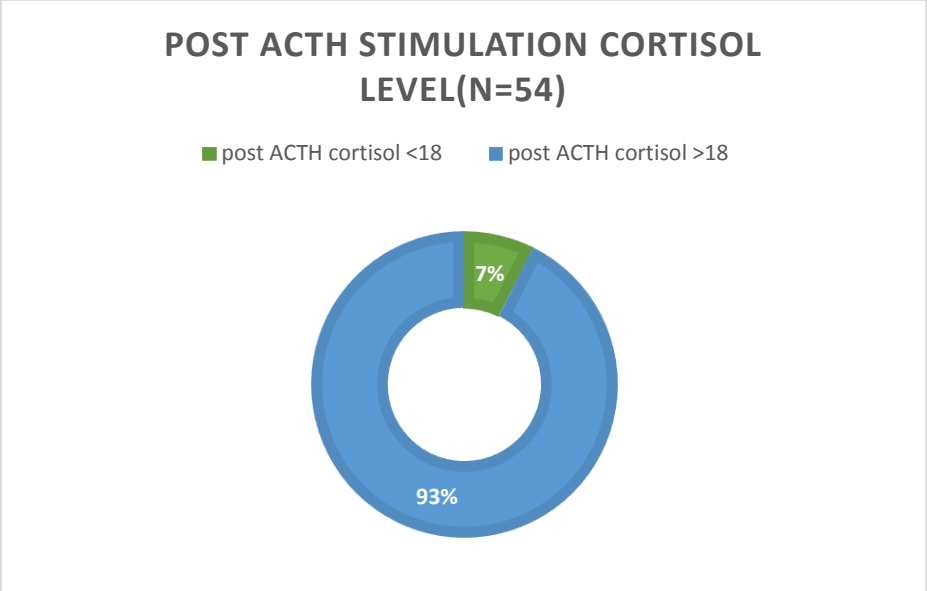
Fig-12 : 8 AM fasting serum cortisol assessment in the study population



Serum cortisol level after ACTH stimulation (n=54)

For the remaining 59 patients, confirmatory test standard dose ACTH stimulation with 250 mcg of acton prolongatum® was warranted. However, five patients were lost to follow-up. Thus ACTH stimulation was performed on 54 (66.6%) subjects. The median (IQR) serum Cortisol levels post ACTH stimulation was 22.45 (20.65, 25.45) mcg/dl. Post ACTH stimulation S. cortisol level < 18 mcg/dl was observed in 4 (7.41 %) patients. It is depicted in figure-13.

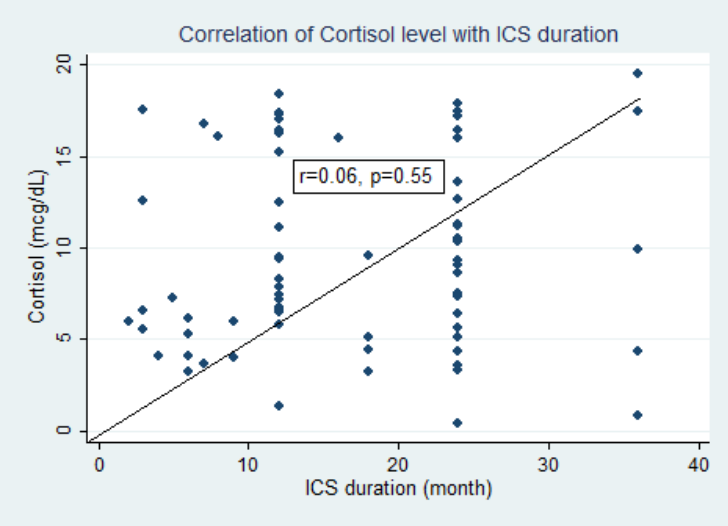
Fig-13 : Post ACTH stimulation serum cortisol among study subjects (n=54)



Correlation between baseline serum cortisol levels with ICS duration

The median (IQR) duration of ICS was 15(12, 24) months among children with fasting 8 AM serum cortisol value ≥15mcg/dl, and 12(12, 24) months among children with cortisol levels < 15mcg/dl. There was no statistically significant correlation between fasting serum cortisol levels and ICS duration (r = 0.06, p =0.5).

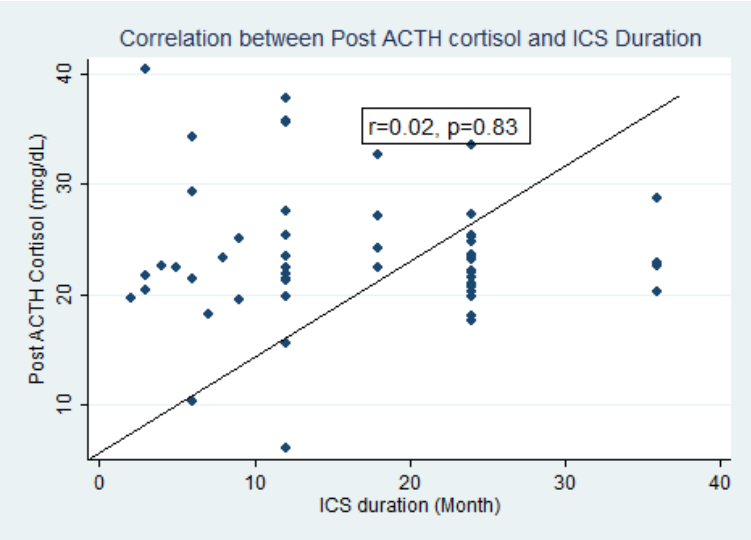
Fig 14: Correlation between baseline Cortisol levels with ICS duration



Correlation between post ACTH stimulation serum cortisol levels with ICS duration

The median (IQR) of ICS duration was 15(9, 24) months among children with post ACTH stimulation serum cortisol value ≥ 18mcg/dl, and 12(9, 18) months among children with post ACTH cortisol levels < 18mcg/dl. There was statistically no significant correlation between post ACTH stimulation serum cortisol and ICS duration (r = 0.02, p = 0.83).

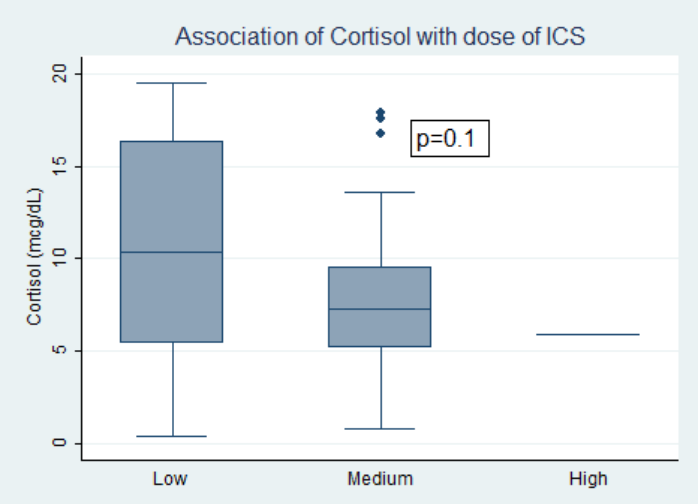
Fig 15. Correlation between post ACTH stimulation serum cortisol (mcg/dl) with ICS use duration



Association between baseline Cortisol levels and ICS Dosage

The Median (IQR) level of cortisol among children with low dose ICS use was 10.39 (5.42, 16.35) mcg/dl, 7.28(5.15, 9.56) mcg/dl with medium-dose, and 5.86(5.81,5.93) mcg/dl with high dose ICS use. There was statistically no significant association between ICS dosage and baseline morning cortisol levels (p = 0.1).

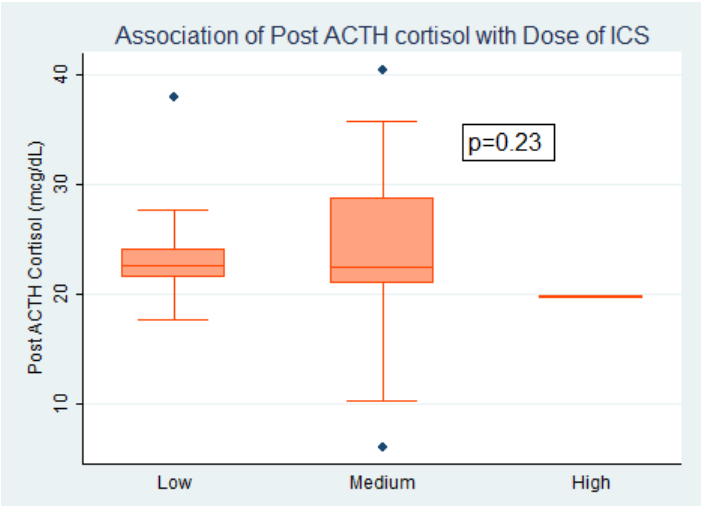
Fig-16: Association between baseline cortisol level and ICS dosage



Association between post-ACTH stimulation S. cortisol and ICS dosage

The Median (IQR) levels of post ACTH stimulation serum cortisol among children with low dose ICS was **22.58 (21.5, 24.19)** mcg/dl, **22.47(20.97, 28.73)** mcg/dl in the medium dose, and **19.73(19.75, 19.80)** mcg/dl in children taking high dose ICS. There was no statistical significance between the association of ICS dosage and post ACTH stimulation serum cortisol levels (p = 0.23).

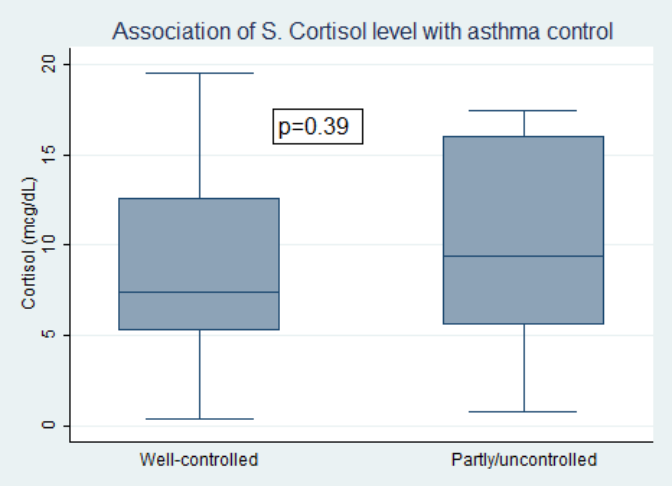
Fig-17: Association between Post ACTH stimulation serum cortisol levels and dosage of ICS



Association of fasting 8 AM cortisol level with asthma control

The median (IQR) value of serum fasting 8 AM cortisol level was 7.42 (5.25, 12.56) in well-controlled children, while it was 9.39 (5.59, 16) in the partly/uncontrolled group. There is no statistically significant association of s. cortisol level with asthma control (p=0.39).

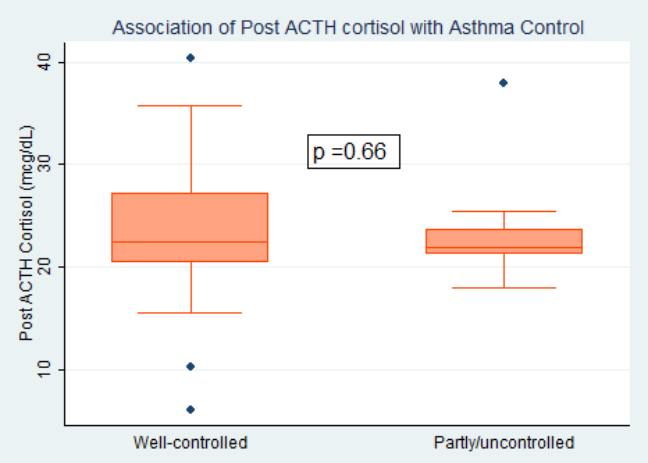
Fig 18- Association between baseline serum cortisol levels and asthma controls



Association between post ACTH stimulation serum cortisol levels and Asthma control

The median (IQR) value of post ACTH stimulation serum cortisol level was 22.52(20.44, 27.18)mcg/dl in well-controlled asthma, while it was 21.87(21.20, 23.77) in partly/uncontrolled group. There is no statistically significant association of s. cortisol level with asthma control (p=0.67).

Fig 19 : Association between post ACTH stimulation serum cortisol levels and asthma control assessed with ACQ score



Secondary objectives

Correlation of ICS Duration with anthropometric parameters

There was statistically no significant correlation between ICS duration and Z score of height (r = 0.06 ; p = 0.5), Z score of weight (r = -0.07; p = 0.5 .) and Z score of BMI (r = -0.02; p = 0.8). These are depicted in Figure 21-23.

Fig-20: Correlation between Z score of height at enrolment and ICS Duration

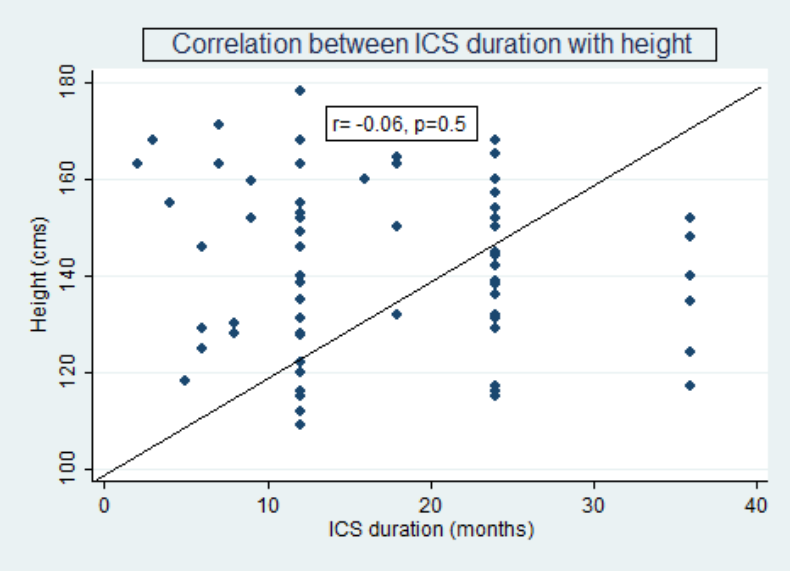


Fig-21: Correlation between Z score of weight at enrolment and ICS Duration

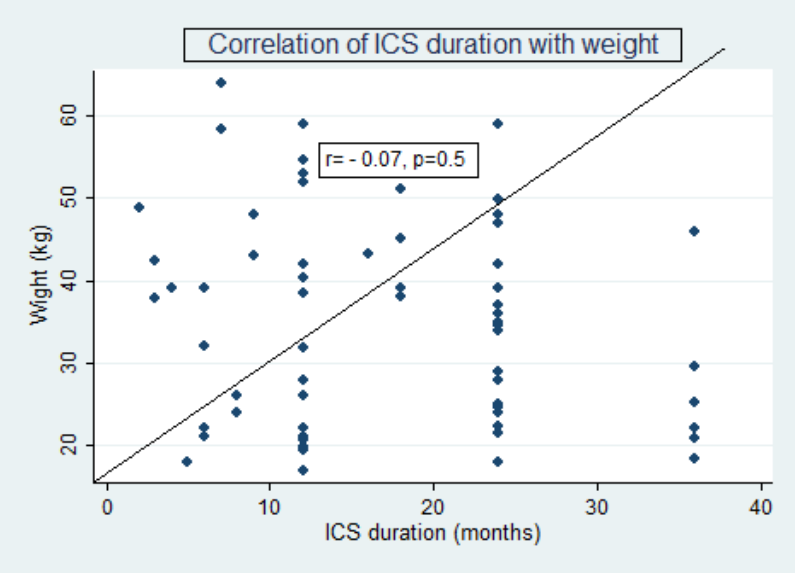
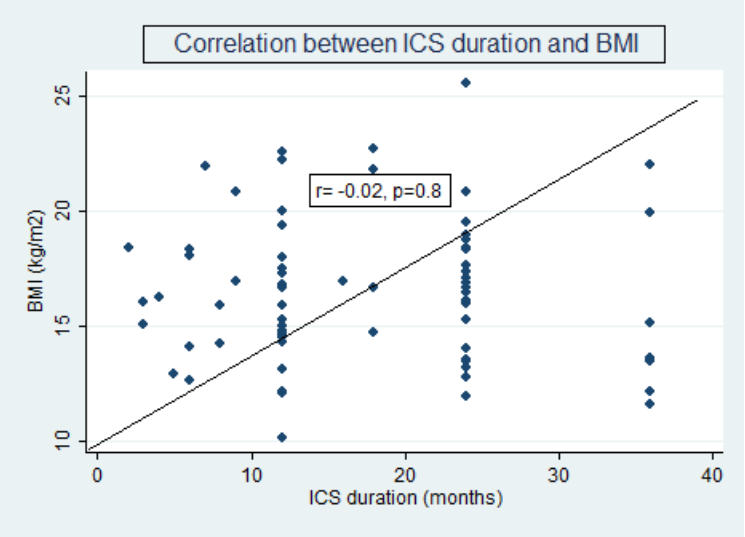


Fig-22: Correlation between Z score of BMI with ICS Duration



Other Complications of Prolonged ICS use:

Only one child (1.2%) had the complaint of halitosis. None of the children had features of other local complications of ICS use, like hoarseness of voice or oral candidiasis. We did not find any other systemic complications of ICS, including moon facies, purplish striae, easy bruisability, and hypertension.

DISCUSSION

This study aimed to assess the effect of prolonged use of ICS on the hypothalamic-pituitary-adrenal axis. For this, we first screened the enrolled children by performing an 8 AM fasting serum cortisol level. Then the ACTH stimulation test was performed in children with low 8 AM cortisol levels. We found that 5.1 % of the children had HPA axis suppression. We did not find any adverse effect of prolonged ICS use on anthropometric parameters in enrolled children.

The HPA axis suppression can be assessed by estimating the 8 AM cortisol level as screnning and subsequently confirmed by the ACTH stimulation test. Some authors have performed only cortisol levels in literature, while others directly performed the ACTH stimulation test. The study by Anuradha et al. (37) and Dorsey et al. (41)had directly performed confirmatory testing of ACTH stimulation.

The cut-off value for morning cortisol level in documenting HPA axis suppression is not uniform in the literature. A Study by O. Cavkaytar (38) took cut-off cortisol levels of 15 mcg/dl to document HPA axis suppression. In a study among adult asthmatic subjects , 8 AM cortisol > 18 mcg/dl ruled out adrenal insufficiency. The Harriet Lane Handbook of pediatrics described a value of 8 AM fasting cortisol levels >14mcg/dl excluding adrenal insufficiency. In this study, we took a cut-off cortisol level of < 15 mcg/dl to document adrenal insufficiency.

In this study, 19/78 (24.4%) children had baseline cortisol levels ≥ 15 mcg/dl, thus ruling out adrenal insufficiency in the screening test itself . The study by O. Cavkaytar et al. (38) reported 31/91 children (34.4%) have normal basal cortisol levels. Similarly, a study by Smith et al. (39) observed 171/214 (79%) children to have normal cortisol levels. This variation in baseline cortisol level may be due to several factors, such as the type of ICS used (MDI vs. DPI), and different demographic profiles.

Estimation of adrenal insufficiency by only morning cortisol level could be misleading. It can be under or overestimating adrenal insufficiency. Hence it should be confirmed with an ACTH stimulation test. The confirmatory test can be performed in several ways, and the insulin tolerance test is considered as the gold-standard test. However, this procedure usually require hospitalization and stringent monitoring, therefore not always feasible in clinical practice. Therefore, researchers have devised

other validated Short ACTH stimulation tests . Studies by, Anuradha et al., O.Cavkaytar, and Smith et al.. had used low dose ACTH stimulation with IV synacthen injection for this purpose. Choi S et al. (40) had performed confirmation with with standard dose of ACTH analogue . In this study, we performed ACTH stimulation test with standard dose of IM Acton Prolongatum. It is a validated method and easy to perform on OPD basis.

We performed an ACTH stimulation test in 54 (69.2%) children who had basal cortisol levels less than 15 mcg/dl. We found adrenal insufficiency (post ACTH cortisol <18 mcg/dl) in 4/54 (7.4%) children making a total prevalence of 5.1% (4/78) in the study population. The prevalence of adrenal insufficiency in asthmatic children was 17/70 (24.3%) by Anuradha et al. (47), while it was 7/60 (7.7%) by O. Cavkaytar.(38) Similarly, a study by Smith et al. (39) had observed a prevalence of 20 % (43/214). Whereas a study in the adult population by Choi s et al. (40) found that more than half of the population (55.3%) had adrenal insufficiency. The reason for this variation in the prevalence of adrenal insufficiency in the study population from other global studies may include – the type of ICS used, study method for confirmation of ACTH stimulation, age of study population, racial factors, etc.

The type of ICS used by all the children enrolled in our study was budesonide. No other study in the literature has the entire study population using the same drug. The study by Choi S et al. (40) have used fluticasone propionate. The doses of other types of ICS were equated to the dosage of fluticasone. Kwda A et al. (36) did not mention the type of ICS being used in her study. Dorsey et al.(41) enrolled children taking budesonide , fluticasone and fluticasone and salmetrol which had 7/22(32%), 9/22(41%), 6/22(27%) distribution of subjects, respectively. The prevalence of adrenal insufficiency in the group taking budesonide was 4/6 (67%). However, the mean dosage intake for the budesonide group was 733 (400 – 1000)mcg/day, which is a high dose according to our study, and there were only two study subjects in our study taking high dose ICS. The study by Smith et al. had only four children in the total study population (n=214) taking budesonide. None of them had HPA axis suppression confirmed by LDAT.

A meta-analysis by Zollner et al. (38) included 22 studies, all done prior to 1988, studied HPA axis suppressive effects of beclomethasone and budesonide. The studies, however, had a small study population ranging from 10 – 22 subjects. The studies

included used a metyrapone challenge test. One study included an insulin tolerance test to assess HPA axis suppression. However, clear descriptions regarding the prevalence of adrenal insufficiency among children using budesonide inhalers were not obtained. The Turkish study by O.cavkaytar (38) had 17.6% of the study population (n=91) were using budesonide. However, they converted the dosages of different types of ICS (including ciclesonide, budesonide, fluticasone, etc.) to equivalents of fluticasone propionate according to NAEPP guidelines, and further analysis was done. Among the group of children taking budesonide, only one patient (6.25%) had HPA axis suppression assessed with LDAT.

Another reason for the different results of our study may be the difference in dosage of ICS used by subjects. Our study defined low, medium, and high dosages with a daily intake of 100 – 200 mcg/day, >200-400 mcg/day, and >400 mcg/ day, respectively. In our study, a maximum number of children were using low dose(51.3%) followed by medium dose (46.15%) and high dose (2.56%). There were 3/36 (8.3%) children in the medium dose group who had adrenal suppression and one child (1/40; 2.5%) among low dose group with HPA suppression. None of the children taking a high dose (n= 2) had adrenal suppression. There was also no significant statistical association between ICS dosage and HPA axis suppression in our study. KWDA A., et al. (36) had 10, 6 and 1 subject out of total 17 subjects with adrenal suppression , using high dose, medium dose and low dose of ICS respectively. There was statistically significant association between the dose of ICS and adrenal suppression ($\chi 2$ =12.291, df =3 ,$p<0.01$). Choi IS et al. (40), also studied the association of ICS dosage with adrenal suppression where it was found that 44.4% of children taking low dose, 58.3% of children with medium dose and 58.7% of children with high dose ICS had adrenal suppression. As they evaluated both budesonide and fluticasone after converting to equivalents of fluticasone propionate according to NAEPP guidelines of 2007, it was found that BMI adjusted daily dose of ≥22 mcg (FP-HFA equivalent) was only found to increase the risk for Adrenal suppression (OR 7.22, p=0.028).

We defined long-term ICS as duration of use >6 months. All children enrolled in the study met this criteria. It was defined similarly in studies by Choi et al (40), KWDA et al (36), and Dorse et al.(41) However, Study by Smith et al included children taking ICS > 3months and O. Cavkaytar et al included childen taking ICS > 6 weeks.

Duration of ICS intake and its association with HPA axis suppression was also assessed in our study. There was no statistically significant association between duration of ICS intake and adrenal suppression. However due to Covid pandemic most of the children stopped ICS intake and restarted later on. Hence duration of ICS use for many children with good compliance in our study was lower than other studies published in literature. There was no association between ICS duration and HPA suppression according to studies by Smith et al (39) and O cavkaytar et al. (38)Anuradha et al (36) reported statistically significant association between ICS duration and HPA axis suppression. The Korean study by Choi IS et al (40) showed that number of subjects with abnormal ACTH stimulation test increased with increase in duration of ICS use but without statistical significance.

Our study also looked into the possibility of any association of asthma control with adrenal axis suppression. Majority of our subjects(72.8%) had well-controlled asthma assessed with ACQ . But there was no association between asthma control and HPA axis suppression. Studies looking into the same association were not obtained from the literature.

Another feature of our study was that all children enrolled were using pressured metered dose nhalers (pMDIs) for the administration of ICS. Any association between ICS inhalation devices and HPA axis suppression was previously looked into , by a Turkish study (38) where 69.2% of their subjects were using pMDIs with spacer and concluded that there was no association ($p = 0.63$) for the same. Similarly, study by Dorsey et al (47) also concluded that there is no significant association between ICS inhaler device and HPA axis suppression.

The secondary objectives of our study included assessment of effect of long term ICS on anthropometric parameters including height, weight an BMI. For the same we documented the height weight and BMI of the children at the time of enrolment, and Z scores of the same parameters were analysed for any association with ICS duration . However we couldn't find any association between the two variables. The effect of long term inhaled corticosteroids on height was also assessed by the study published in 2019 , were also , no statistically significant association was found. The meta analysis of 16 studies published in 2015 (48) found that there was significant decreasein growth velocity at one year follow up and a high quality RCT showed final

adult height reduction of -1.2cm in Budesonide vs placebo. But we did not measure he growth velocity of the subjects in our study.

None of our subjects, both with normal HPA axis and with suppression, had any evidence of local complications including hoarseness in voice/ voice changes/ oral candidiasis. However, 1 child had the compliant of halitosis. None of the children with HPA axis suppression had any symptoms suggesting adrenal insufficiency including fatigue, hypoglycemia, syncopal attacks, abdominal pain and headache. No one had abdominal striae, easy bruisability or hypertension suggesting that the systemic effect ICS is minimal.

The technique of ICS use in study population was also assessed. All the children in our study were taking ICS with pMDIs and majority (97.4%) were using spacer. 66.6% of children were rinsing their mouth after ICS use also. This might be one of the reason for absence of local complications including dysphonia and oral candidiasis as compared to older studies in literature. The type of ICS used also is considered to influence the development of local complications. Although meta analysis by Rachelefsky (10)has reported 1-6% subjects to have dysphonia with budesonide, Tuzuner et al (49) stated no effect on voice after 1 month of 800 mcg/day budesonide use.

STRENGTH AND LIMITATIONS OF THE STUDY

Strength of study

- We enrolled only Physician diagnosed cases of asthma as per the GINA guideline.
- We enrolled all children irrespective of doses of ICS
- We used a validated method for the ACTH stimulation test
- We tried to assess correlation of asthma control and adrenal insufficiency also.
- To the best of our knowledge, it is the first kind of study among asthmatic children from India.

Limitation of Study

- The number of children using high dose Inhaled corticosteroids were low (2.56%) in the study population
- Due to COVID Pandemic, we could not follow these children to document the effects of prolonged use of ICS on growth velocity.

CONCLUSION

We conclude that there is no significant effect of long term inhaled corticosteroids used in low dose and moderate dose on hypothalamo-pituitary adrenal axis. Asthma control also doesnot have any influence in causing secondary adrenal insufficiency in children with asthma who are using ICS. The drug has only little effect on growth parameters of children including height, weight and BMI and doesnot cause any local or systemic complications . However further studies with more number of children using higher doses of ICS is required .

SUMMARY

Title of the study: Effect of long-term inhaled corticosteroids on the hypothalamic-pituitary-adrenal axis in children with asthma.

Background: Inhaled corticosteroids is the cornerstone in management of asthma in children and the most commonly used being budesonide in India. Local and systemic adverse effects of ICS have been reported and one of the potentially dangerous adverse effect is secondary adrenal insufficiency due to HPA axis suppression. There are few studies which assessed the ability of ICS to cause HPA axis suppression that too using a validated confirmatory test. Also there were no studies looking into the same , among Indian population. Hence this study was carried out to assess the HPA axis suppression caused by long term use of ICS.

Objectives: The primary objective of this study was to assess the effect of long term (>6 months) inhaled corticosteroids on hypothalamic-pituitary-adrenal axis in children with asthma.

The secondary objectives included

- to assess the effect of long term inhaled corticosteroids on growth parameters like height, weight, BMI ;
- presence of any local effects of ICS including hoarseness of voice, oral candidiasis, halitosis;
- presence of any systemic features like hypertension , easy bruisability , skin thinning, moon facies.;

Methodology: We performed a cross-sectional study after ethical clearance from the institute's ethical committee. Data regarding demographic details, asthma related details, technique of ICS use, compliance, asthma control (using GINA and ACQ), and clinical examination for any local or systemic complications. Firstly, A 8 AM fasting serum cortisol samples were taken. Those children who had a value ≥15 mcg/dl were labelled to have normal HPA axis whereas those having baseline serum cortisol level <15mcg/dl were subjected ACTH stimulation test. In this test, we injected 250 mcg synthetic ACTH (Acton Prolongatum ®) via IM route, and serum cortisol levels was assessed after 60 minutes.

Results: We screened a total of 270 children, and 81 children were enrolled. Due to technical errors, baseline cortisol samples of three children were not enrolled and a total of 78 children were taken for further analysis. The median age group of the study population was 11.5(8,14) years ; 55 % were boys and 23% were girls. Median (IQR) of ICS use was 12(12, 24) and age of diagnosis of asthma was 6(5,9)years.Among the study population, 40/78(51.3%) were taking low dose where as 36/78(46.2%) and 2/78(2.56%) were taking medium and high dose of ICS respectively. Asthma was well controlled according to ACQscore for 56/78(71.8%) children and was partly/poorly controlled for 22/78(28.2%) children.

19 children (24.3%) had baseline cortisol levels >15 mcg/dl. Out of the 59 children that warranted confirmatory test for adrenal insufficiency, 6 were lost to follow up. A standard dose ACTH stimulation test was performed in 54 children. 4 children (7.4%) had post ACTH serum cortisol values <18mcg/dl. There were no stastically significant association between baseline cortisol with ICS dose (p=0.1), duration (p=0.5) or Asthma control (p=0.39). Similarly no association was found between post ACTH serum cortisol measurement and ICS dosage (p=0.23), duration(p=0.83) or asthma control(p=0.67). There were no statistically significant association between ICS dosage, duration of use , asthma control with baseline cortisol levels, or post ACTH stimulation cortisol levels. There was no significant association between anthropometric parameters and ICS duration The p value of correlation between ICS duration and Z score of height, weight and BMI were 0.5,0.5 and 0.8 respectively. One child (1.28%) had the complaint of halitosis, other than that none of the children had any local complications of ICS, including hoarseness of voice or oral candidiasis; or other systemic complications like hypertension, easy bruisability, skin thinning, or moon facies

Conclusion: We conclude that there is no significant effect of ICS especially low and medium doses with prolonged use on HPA axis. There was no effect on anthropometric parameters with ICS use and there was no evidence of any other systemic or local complications among the study population. Thus concluding that ICS is a safe drug that can be used in low/ moderate doses for long duration, without any dangerous side effect of secondary adrenal insufficiency and more studies are warranted to establish the effect of high doses (>400 mcg/day) of ICS on HPA axis.

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APPENDIX-1

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation : **Effect of inhaled corticosteroids on hypothalamic pituitary Adrenal axis in children with asthma**

Name of PG Student : Dr. Lekshmi SH (Tel. No. 8075566113)
Patient/Volunteer Identification No. : _____
I, _____ M/o or F/o _____
R/o _____
give my full, free, voluntary consent for my child to be a part of the study, "EFFECT OF INHALED CORTICOSTEROIDS ON HYPOTHALAMO PITUITARY ADRENAL AXIS IN CHILDREN WITH ASTHMA" the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.
I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.
I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____ (Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.
Date: _____ _____
Place: _____ Signature/Left thumb impression
This to certify that the above consent has been obtained in my presence.
Date: _____ _____
Place: _____ Signature of PG Student

1. Witness 1
2. Witness 2

_____ _____
Signature Signature
Name: _____ Name: _____

Address: _____ Address: _____
_____ _____

APPENDIX -2

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र थीसिस / शोध प्रबंध का शीर्षक: अस्थमा के साथ बच्चों में हाइपोथैलेमिक पिट्यूटरी अधिवृक्क अक्ष पर साँस की कॉर्टिकोस्टेरॉइड का प्रभाव

पीजी छात्र का नाम: डॉ. लीक्ष्मी एसएच (दूरभाष संख्या 8075566113)

रोगी / स्वयं सेवक पहचानसंख्या: _____

मैं, _____M / o या F / o _____

निवास_____

मेरे बच्चे को अध्ययन का एक हिस्सा बनने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति दें। ASTHMA के साथ चिल्ड्रेन में हाईपोथेल्मिक एडिशनल एक्सिस में हाइपोथेलामो पर इनहेल्ड CORTICOSTEROIDS का प्रभाव ”

जिस की प्रक्रिया और प्रकृति मुझे अपनीपूर्ण भाषा में बताई गई है ।मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।

मैं समझताहूं कि मेरी भागी दारी स्वैच्छि कहै और बिना किसी कारण के किसी भी समय अध्यय नसे बाहर निकलने के मेरे अधिकार से अवगत हूं।

मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारीको _____ (कंपनी का नाम) यानि यामक अधिकारियों के जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

दिनांक : _____ _____

जगह : _____ हस्ताक्षर / बाएंअंगूठेकानिशान

यह प्रमाणित करनेके लिए किमेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

दिनांक: _____ _____

जगह : _____ पीजीछात्रकेहस्ताक्षर

साक्षी 1 साक्षी 2

_____ _____

हस्ताक्षर हस्ताक्षर

नाम : _____ नाम: _____

पता: _____ पता: _____

APPENDIX- 3

PARTICIPANT INFORMATION SHEET (PIS)

Title of the Study/Project: "EFFECT OF INHALED CORTICOSTEROIDS ON HYPOTHALAMIC PITUITARY ADRENAL AXIS IN CHILDREN WITH ASTHMA"

- **Aims and purpose of the research:** To look for the effect on hypothalamo pituitary adrenal axis in children of age 5-18 years who are diagnosed cases of asthma under treatment with inhaled corticosteroids for a minimum of 6 months.

i) **Procedure:** Your child is invited to join the study. It is planned to include all such children with asthma taking inhaled corticosteroids in this study. The assessment shall include recording of relevant history and clinical examination findings. 2ml venous sample will be taken at 8 am in empty stomach along with other necessary investigations. If your childs S. Cortisol value is below normal value , you will be asked to review once more in OPD when another confirmatory test will be carried out (ACTH stimulation test), where one venous sample will be taken at 0 hour, an IM injection of ACTH (250 MCG) will be given followed by repeat sample of 2ml after 1 hour

ii) **Expected duration of the subject participation-** One or two visit

iii) **The benefits to be expected from the research to the subject or to others:** Knowing whether your child is having any impact on his/her adrenal glands due to use of inhaled corticosteroids; early detection of occult adrenal suppression in child; the study will help to ascertain the safety of ICS.

iv) **Any risk to the subject associated with the study:** Potentially none.

v) **Maintenance of confidentiality of records:** The medical records of the patient shall be kept confidential and accessed only by the treating physician or, if necessary, by the Ethics Committee of the All India Institute of Medical Sciences, Jodhpur.

vi) **Provision of free treatment, compensation for research related injury:** Not applicable

vii) **Freedom of individual to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled:** You are free to participate in and withdraw from this study at any time you so desire. This will in no way affect your ongoing treatment at the Institute.

viii) **Costs and source of investigation:** Investigations mentioned will be done in AIIMS, you are not expected to pay for cost of this investigation.

ix) **Telephone number/contact number of Principal Investigator and Co investigator:** In case of any concerns related to your child's treatment, you should contact:

Dr. Prawin Kumar, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan; 342005; Phone 9540084230, email: drprawin484@gmail.com

Dr. Lekshmi SH, PG student, Department of pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, 342005; Phone:8075566113 Email- lekshmi.s.h.nair@gmail.com

x) It is certified that translation to vernacular is accurate.

APPENDIX- 4

आंशिक सूचना शीट

i) अध्ययन / परियोजना का शीर्षक: अक्ष वाले बच्चों में हाइपोथैलामो- पट्यूटरी-अ धवृक्क अक्ष पर साँस की कॉर्टिकोस्टेरॉइड का प्रभाव

ii) **अनुसंधान का उद्देश्य**: **प्रक्रिया:** 5-18 वर्ष के बच्चों में हाइपोथैलामो पिट्यूटरी अधिवृक्क अक्ष पर प्रभाव देखने के लिए, जिन्हें कम से कम 6 महीने के लिए साँस की कॉर्टिकोस्टेरॉइड के साथ उपचार के तहत अस्थमा के मामलों का निदान किया जाता है।

iii) **प्रक्रिया:** आपके बच्चे को अध्ययन में शामिल होने के लिए आमंत्रित किया जाता है। इस अध्ययन में ऐसे सभी बच्चों को शामिल करने की योजना बनाई गई है, जो साँस में कॉर्टिकोस्टेरॉइड लेते हैं। मूल्यांकन में प्रासंगिक इतिहास और नैदानिक परीक्षा निष्कर्षों की रिकॉर्डिंग शामिल होगी। 2ml शिरापरक नमूना सुबह 8 बजे खाली पेट और अन्य आवश्यक जांच के साथ लिया जाएगा। यदि आपकी चिल्ड एस। कॉर्टिसोल वैल्यू सामान्य मूल्य से कम है, तो आपको ओपीडी में एक बार फिर से समीक्षा करने के लिए कहा जाएगा, जब एक और पुष्टिकर परीक्षण किया जाएगा (एसीटीएच उत्तेजना परीक्षण), जहां एक शिरापरक नमूना 0 घंटे में लिया जाएगा, एक आईएम इंजेक्शन ACTH (250 MCG) को 1 घंटे के बाद 2 ml का रिपीट नमूना दिया जाएगा

iv) **भागीदारी की अपेक्षित सहभगिति** - एक या दो मुलाक़ात

v) **शोध सेआपको या दुसरो के लिए अपेक्षित लाभ**: यह जानना कि क्या आपका बच्चा साँस की कॉर्टिकोस्टेरॉइड्स के उपयोग के कारण उसकी / उसके अधिवृक्क ग्रंथियों पर नकारात्मक प्रभाव डाल रहा है, बच्चे में मनोगत अधिवृक्क दमन का शीघ्र पता लगाने; अध्ययन से आईसीएस की सुरक्षा का पता लगाने में मदद मिलेगी

vi) **अध्ययन से जुड़े विषय पर कोई जोखिम**: संभावित रूप से कोई नहीं।

vii) **अभिलेखों की गोपनीयता का रख-रखाव:** रोगी के मेडिकल रिकॉर्ड को गोपनीय रखा जाएगा और इलाज चिकित्सक द्वारा या यदि आवश्यक हो, तो अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर की आचार समिति द्वारा किया जाएगा।

viii) **मुफ्त इलाज का प्रावधान, अनुसंधान से संबंधित चोट के लिए मुआवजा:** लागू नहीं

ix) **किसी भी समय अनुसंधान से पीछे हटने की स्वतंत्रता, दंड या लाभ के नुकसान के बिना:** आप इस इच्छा से किसी भी समय इस अध्ययन से भाग लेने और वापस लेने के लिए स्वतंत्र हैं। यह किसी भी तरह से संस्थान में आपके चल रहे उपचार को प्रभावित नहीं करेगा।

x) **लागत और जांच का स्रोत:** उल्लिखित जांच एम्स में की जाएगी, आपको इस जांच की लागत के लिए भुगतान नहीं करना होगा।

xi) **प्रधान अन्वेषक और सह अन्वेषक के टेलीफोन नंबर / संपर्क नंबर**: आपके बच्चे के उपचार से संबंधित किसी भी चिंता के मामले में, आपको संपर्क करना चाहिए:

<u>डॉ। प्रवीण कुमार</u> अतिरिक्त प्रोफेसर, बाल रोग विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान-342005; फोन 8475000270,

डॉ। लीक्ष्मी एसएच

पीजी छात्र, बाल रोग विभाग,

अखिल भारतीयआयुर्विज्ञान संस्थान,जोधपुर, राजस्थान-342005;

फोन: 8075566113 ईमेल- lekshmi.s.h.nair@gmail.com

xi) यह प्रमाणित हो गया है कि अनुवाद में शब्दशः तक सटीक है।

APPENDIX- 5

Enrolment Form

STICKER

Enrollment number	
UHID	
Date:	

PURPOSE OF THE FORM: • This form is meant to be filled only if the patient satisfies all the criteria mentioned in screening form.			
Part A: Baseline characteristics of the patient			
S. No.	**Items**		**Response**
1.	Name		
3.	Age (completed years)		
4.	Gender (Male=1/female=2)		
12.	Address 1:		
	1.Urban ;2. rural		
14	Contact numbers	Landline	
		Mobile 1	
		Mobile 2	

Part A 1: History and Details of disease		
S. No.	**Items**	**Response (yes=1/No=2)**
1.	Age of diagnosis of asthma	
2.	Last dose duration	
2.	Total Duration since starting of ICS	

3.	Current treatment : 1. Budecort (100)- 1 puff BD 2. Budecort (100) 2 puff BD 3. Budecort (100) 3 puff BD 4. FORACORT (100) 1 puff BD 5. Foracort (100) 2 puff BD 6. Foracort (100) 3 puff BD	
3.	ACQ score	
4.	H/o any recent acute exacerbation of asthma(in past 4 weeks) yes=1/no=2	
5	History of absence of height gain Present=1/absent=2	
6.	History of excessive weight gain Present=1/absent=2	
7.	History of easy bruising (present = 1, absent = 2	
8.	History of any symptoms of adrenal suppression including – 1.anorexia 2. nausea 3. Fatigue 4. head ache 5. abdominal pain 6.myalgia/arthralgia 7. behavioral abnormalities	
8.	Is there good compliance to ICS ? YES=1/ NO = 2	
9.	Time to finish one canister	
10.	H/o halitosis yes=1/no=2	
11.	h/o any voice changes (hoarseness of voice)	
12	Use of spacer ? Present=1/absent=2	
13	does the child have a habit of rinsing mouth after using ICS ? Yes = 1/ no=2	
14	History of any other endocrinological disease? yes=1 no=2	

15	Use of oral corticosteroid in past 4 weeks? **(Y=1/N=2)**	
16.	h/o any other co morbidities	
	If yes, MENTION.	

Examination			
Part B1: Vitals and GPE			
		Current	Previous value (first visit)
1	Blood Pressure		
2.	Purplish striae		
3	Moon facies		
4	Evidence of easy bruisability		
5	Oral candidiasis		
Part B 2: Anthropometry			
	Items	Current	previous value (first visit)
1.	Height		
	IAP Z score		
2.	Weight		
	IAP Z score		
3.	BMI (kg/m^2)		
	IAP Z score		
4.	SMR STAGE		
5.			

Part B3: Systemic Examination	
Respiratory system	
Others significant findings	

Part B4: Investigations	
S.cortisol @ 8 am	
Post ACTH stimulation, S.Cortisol	

APPENDIX- 6

Asthma Control Questionnaire (ACQ) score

दमा नियंत्रण प्रश्नावली (ACQ)

HINDI VERSION FOR INDIA

अधिक जानकारी के लिए:

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Senior Translator: Dr. Hem Raj Pal, M.D.

MAY 2017

ACQ - India/Hindi - Version of 18 May 17 - Mapi.
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दमा नियंत्रण प्रश्नावली ©
(HINDI VERSION FOR INDIA)

रोगी परिचय _____

अतिथि / दिनांक _____

कृपया 1 – 6 प्रश्नों के उत्तर दें।

जवाब की उस संख्या को **घेरें** जो सबसे बेहतर रूप से ये बयान करती हो कि आप पिछले हफ्ते में कैसे रहें।

1. पिछले हफ्ते में, औसतन कितनी बार **दमे की वजह से आप रात में जग** गए?
   - 0 कभी नहीं
   - 1 शायद ही कभी
   - 2 कुछ बार
   - 3 कई बार
   - 4 बहुत बार
   - 5 अत्यधिक बार
   - 6 दमे की वजह से सो नहीं पाता

2. पिछले हफ्ते में, औसतन **जब आप सवेरे उठते थे तो दमे के लक्षण कितने ज़्यादा खराब थे**?
   - 0 कोई लक्षण नहीं
   - 1 बहुत हल्के लक्षण
   - 2 हल्के लक्षण
   - 3 कुछ (मध्यम) लक्षण
   - 4 थोड़े गंभीर लक्षण
   - 5 गंभीर लक्षण
   - 6 बहुत गंभीर लक्षण

3. पिछले हफ्ते में, सामान्यत: दमे की वजह से आप **अपनी क्रियाओं** (जैसे घरेलू, स्कूल संबंधी, कार्य संबंधी इत्यादि) **में कितने सीमित रहे** हैं?
   - 0 बिलकुल सीमित नहीं
   - 1 बहुत थोड़े सीमित
   - 2 थोड़े सीमित
   - 3 कुछ (मध्यम) सीमित
   - 4 बहुत ज़्यादा सीमित
   - 5 अत्यधिक सीमित
   - 6 संपूर्णतया सीमित

4. पिछले हफ्ते में, सामान्यत: दमे की वजह से आपको **साँस फूलने** का अनुभव कितना हुआ?
   - 0 बिल्कुल नहीं
   - 1 बहुत कम
   - 2 कम
   - 3 कुछ (मध्यम) ज़्यादा
   - 4 बहुत ज़्यादा
   - 5 बहुत बहुत ज़्यादा
   - 6 अत्यधिक ज़्यादा

दमा नियंत्रण प्रश्नावली ©
(HINDI VERSION FOR INDIA)

रोगी परिचय _____

अतिथि / दिनांक _____

कृपया 1 – 6 प्रश्नों के उत्तर दें।

जवाब की उस संख्या को **घेरें** जो सबसे बेहतर रूप से ये बयान करती हो कि आप पिछले हफ्ते में कैसे रहें।

1. पिछले हफ्ते में, औसतन कितनी बार **दमे की वजह से आप रात में जग** गए?
   - 0 कभी नहीं
   - 1 शायद ही कभी
   - 2 कुछ बार
   - 3 कई बार
   - 4 बहुत बार
   - 5 अत्यधिक बार
   - 6 दमे की वजह से सो नहीं पाता

2. पिछले हफ्ते में, औसतन **जब आप सवेरे उठते थे तो दमे के लक्षण कितने ज़्यादा खराब थे**?
   - 0 कोई लक्षण नहीं
   - 1 बहुत हल्के लक्षण
   - 2 हल्के लक्षण
   - 3 कुछ (मध्यम) लक्षण
   - 4 थोड़े गंभीर लक्षण
   - 5 गंभीर लक्षण
   - 6 बहुत गंभीर लक्षण

3. पिछले हफ्ते में, सामान्यत: दमे की वजह से आप **अपनी क्रियाओं** (जैसे घरेलू, स्कूल संबंधी, कार्य संबंधी इत्यादि) **में कितने सीमित रहे** हैं?
   - 0 बिलकुल सीमित नहीं
   - 1 बहुत थोड़े सीमित
   - 2 थोड़े सीमित
   - 3 कुछ (मध्यम) सीमित
   - 4 बहुत ज़्यादा सीमित
   - 5 अत्यधिक सीमित
   - 6 संपूर्णतया सीमित

4. पिछले हफ्ते में, सामान्यत: दमे की वजह से आपको **साँस फूलने** का अनुभव कितना हुआ?
   - 0 बिल्कुल नहीं
   - 1 बहुत कम
   - 2 कम
   - 3 कुछ (मध्यम) ज़्यादा
   - 4 बहुत ज़्यादा
   - 5 बहुत बहुत ज़्यादा
   - 6 अत्यधिक ज़्यादा

APPENDIX- 7

Ethical clearance certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2051 Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/969**

Project title: **"Effect of long term inhaled corticosteroids on hypothalamic- pituitary adrenal axis in children with asthma"**

Nature of Project:	**Research Project**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr.Lekshmi S H**
Guide:	**Dr.Prawin Kumar**
Co-Guide:	**Dr.Kuldeep Singh, Dr.Jagdish Prasad Goyal & Dr.Varuna Vyas**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, **Website:** www.aiimsjodhpur.edu.in, **Phone:** 0291-2740741 Extn. 3109
Email: ethicscommittee@aiimsjodhpur.edu.in

MASTER CHART

ID	Age	Gender	residence/ urban 1 rural- 2	district	S. Cortisol date	S. Cortisol (value)	ACTH stimulation	daily dose and type of ICS	type of dose	Last dose duration (with good compliance)	age of diagnosis of asthma	ACQ Score	GINA Score	Acute exacerbation in 4 weeks	Absence of ht gain 1= Yes 2= No	Excessive weight gain 1 = yes, 2= no	easy bruisabiliyt	Any other symptoms	compliance to ICS	Duration for one canister	halitosis 1= yes, 2= no	use of spacer 1= yes 2= no	rinses mouth 1= yes 2= no	other endocrinological disease	use of OCS in 4 weeks	purplish striae	moon facies	evidence of easy bruisability	oral candidiasis yes=1 no =2	height first visit	Z score Height first visit	height current visit	Z Score height	weight first visit	Z score weight	weight current visit	Zscore
1	12	Male	1	jodhpur	01-04-21	3.23	22.42	budecort 2	low	18 months	9	Well controlled	well controlled	2	2	2	2	0	good	6 WEEKS	2	1	1	2	2	2	2	2	2	143.7	0.78	150	1.04	43	0.45	51	1.06
2	12	Female	1	Jodhpur	11-01-21	4.033	19.46	foracort 2(	low	9 months	6	Well controlled	well controlled	2	2	2	2	0	GOOD	6 WEEKS	2	1	1	2	2	2	2	2	2	135.7		152	0.48			48	-0.04
3	11	Male	2	Jodhpur	25-01-21	4.32	22.58	foracort 2(	low	36 months	6	Well controlled	well controlled	2	1	2	2	0	good	12 weeks	2	1	1	2	2	2	2	2	2	144	0.18	148	0.24	25	-1.5	25.3	-1.5
4	15	Male	1	jodhpur	11-02-21	3.65	18.24	foracort 4(	medium	7 months	9	Well controlled	well controlled	2	2	2	2	0	good	6 weeks	2	1	1	2	2	2	2	2	2	170	2.82	171	2.99	57.5	1.55	64	2.88
5	17	Male	2	nagaur	15-02-21	9.416	25.45	foracort 4(	medium	12 months	8	moderately controlled	well controlled	2	2	2	2	0	poor	12 weeks	2	1	1	2	2	2	2	2	2			178	2.3	45	-0.29	53	0.89
6	14	Male	2	barmer	04-02-21	5.077	27.18	budecort 2	low	18 months	12	Well controlled	well controlled	2	2	2	2	0	poor	12 weeks	2	1	2	2	2	2	2	2	2	145	-0.4	163	-0.19	33.5	-0.4	39	-1.42
7	7	Male	2	jodhpur	19-02-21	11.2	23.32	foracort 2(	Low	24 months	5	moderately controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	108	-0.42	117	-0.64	15	-1.51	18	-1.19
8	14	Male	1	jodhpur	19-02-21	7.507	23.22	foracort 4(	medium	24 months	9	Well controlled	well controlled	2	2	2	2	0	good	3 weeks	2	1	1	2	2	2	2	2	2			138	1.83			29	0.74
9	12	Female	1	jodhpur	18-02-21	9.912	20.25	foracort 2(	low	36 months	10	well controlled	well controlled	2	2	2	2	0	good	5 weeks	2	1	1	2	2	2	2	2	2	144		152	-1.53			46	-0.46
10	13	Male	2	nagaur	19-02-21	5.147	20.65	foracort 4(	medium	24 months	8	Well controlled	well controlled	2	1	2	2	0	good	5 weeks	2	1	2	2	2	2	2	2	2	142	-1.93	144	-1.93	22	-2.92	24.8	-3
11	7	Male	2	Pali	18-02-21	0.81		foracort 4(	Medium	36 months	4	moderately controlled	well controlled	2	2	2	2	0	poor	12 weeks	2	1	2	2	2	2	2	2	2	110	-1	117	-1.33	16.2	-0.98	18.4	-1.42
12	10	Male	1	jodhpur	19-02-21	9.3	25.46	foracort 4(	medium	24 months	4	Well controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	117	-0.34	131	-0.93	19	-0.9	24	-1.24
13	11	Female	1	jodhpur	19-02-21	3.554	20.97	foracort 4(	medium	24 months	8	poorly controlled	poorly controlled	2	2	2	2	0	poor	8weeks	2	2	2	2	2	2	2	2	2	148		152	0.52	35	2.17	59	1.78
14	15	Male	2	jodhpur	09-11-20	16		budecort 2	low	16 months	6	moderately controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	151	2.42	160	2.03	36	1.11	43.3	-1.08
15	16	Male	2	nagaur	15-02-21	16.76		foracort 4(	medium	7 months	7	moderately controlled	partly controlled	2	2	2	2	0	poor	8weeks	2	1	1	2	2	2	2	2	2			163	1.01	52	-0.86	58.3	-0.13
16	17	male	1	jodhpur	27-02-21	12.45		foracort 4(	medium	12 months	14	moderately controlled	partly controlled	2	2	2	2	0	good	8 weeks	2	1	1	2	2	2	2	2	2			168	1.55	51	1.04	54.7	-0.85
17	5	Male	1	jodhpur	25-02-21	10.35	22	budecort 1	low	24 months	4	Well controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	112	2.9	116	3.08	17.5	1.74	21.5	2
18	10	Male	1	jodhpur	20-02-21	17.45		foracort 2(	Low	36 months	6	poorly controlled	poorly controlled	2	2	2	2	0	poor	6 weeks	2	1	2	2	2	2	2	2	2	137	2.84	140	2.22	24.3	1.23	29.6	1.55
19	12	Female	1	jodhpur	09-09-21	15.97		foracort 2(	Low	24 months	6	Well controlled	well controlled	2	2	2	2	0	good	8 weeks	2	2	2	2	2	2	2	2	2			152	-0.03			48	0.46
20	15	Female	1	jodpur	09-09-21	4.064	22.6	100	low	4 months	7	Well controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	131	0.45	155	1.08	26.2	-1.32	39	0.46
21	8	Male	2	OSIAN	26-02-21	1.374	27.65	BUDECORT	Low	12 months	4	Well controlled	well controlled	2	2	2	2	0	poor	20 weeks	2	1	1	2	2	2	2	2	2	121	3.54	140	2.29	19	1.17	19.9	2.08
22	6	Male	1	Jodhpur	20-02-21	7.139	15.6	Budecort 4	medium	12 months	5	Well controlled	well controlled	2	2	2	2	0	good	8 weeks	2	1	2	2	2	2	2	2	2	106	-1.01	109	-1.34	15	-1.44	17	-1.69
23	9	Male	1	Jodhpur	07-01-21	0.414		foracort 2(	Low	24 months	6	Well controlled	well controlled	2	2	2	2	0	good	7 weeks	2	1	1	2	2	2	2	2	2	140	1.63	144	1.81	30	0.76	36	1.11
24	8	Female	1	Jodhpur	07-01-21	7.326	21.55	forcort 40	medium	24 months	6	poorly controlled	poorly controlled	2	2	2	2	0	ggod	6 weeks	2	1	1	2	2	2	2	2	2	133	0.45	136	0.74	33	1.09	36	1.1
25	14	Male	2	jodhpur	29/6/21	5.93	19.75	foracort 1	high	2 months	3	Well controlled	well controlled	2	2	2	2	0	good	3 weeks	2	1	1	2	2	2	2	2	2	145	0.88	163	0.25	40	1.04	48.8	1.25
26	10	Male	2	Barmer	29-06-21	9.04	21.54	foracort 2(	Low	24 months	5	poorly controlled	poorly controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	133	1.06	139	0.26	26	0.23	24.6	-1.16
27	12	Male	2	jodhpur	03-08-21	17.9		foracort 4(	medium	24 months	7	Well controlled	well controlled	2	2	2	2	0	poor	12 weeks	1	1	2	2	2	2	2	2	2	140	-0.43	144	-0.58	32	-0.34	36	-0.34
28	15	male	1	jodhpur	19/2/21	6.56	20.44	foracort 1(	low	3 months	13	Well controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	1	2	2	2	2	2	2	164	1.6	168	1.75	40	0.7	42.4	0.92
29	5	male	2	jodhpur	24/08/21	3.23	10.32	budecort 4	medium	6 months	5	Well controlled	well controlled	2	1	2	2	0	good	8 weeks	2	1	2	2	2	2	2	2	2	145	-1.8	146	-1.8	36	-0.99	39	0.46
30	13	male	1	jodhpur	13/08/21	6.42	20.33	foracort 4(	medium	24 months	6	Well controlled	well controlled	2	2	2	2	0	good	6weeks	2	1	1	2	2	2	2	2	2	156	0.44	160	0.56	42	0.73	48	0.76
31	15	male	2	jodhpur	14/08/21	11.3	27.28	foracort 2(	low	24 months	10	Well controlled	well controlled	2	2	2	2	0	good	8 weeks	2	1	2	2	2	2	2	2	2	157	0.23	157	0.23	38.5	0.55	42	0.63
32	13	male	2	pali	15/9/21	13.6		foracort 4(	medium	24 months	12	poorly controlled	poorly controlled	2	2	2	2	0	poor	8 weeks	2	1	1	2	2	2	2	2	2	110	-1.54	142	-1.55	29	-0.83	35	-0.91
33	5	MALE	1	JODHPUR	16-06-21	17.28		Foracort 2	Low	12 months	8	moderately controlled	well controlled	2	2	2	2	0	poor	8 weeks	2	1	2	2	2	2	2	2	2	122	1.32	122	1.32	22	0.75	22	0.75
34	13	Female	2	jodhpur	09-06-21	16.4		foracort 2(	Low	12 months	7	well controlled	well controlled	2	2	2	2	0	good	6 weeks	2	1	1	2	2	2	2	2	2	151	1.23	155	1.42	38	0.88	40.3	0.94
35	11	male	2	jodhpur	09-06-21	7.87	21.22	foracort 4(	medium	12 months	5	well controlled	well controlled	2	2	2	2	0	good	7 weeks	2	1	2	2	2	2	2	2	2	114	1.03	116	1.2	19	1.22	19.5	0.89
36	14	male	2	jodhpur	22/7/21	15.2		foracort 2(	low	12 months	5	moderately controlled	well controlled	2	2	2	2	0	poor	6 weeks	2	1	1	2	2	2	2	2	2	144	-0.54	152	-0.4			52	0.56
37	11	mALE	1	jodhpur	02-09-21	16.31		foracort 2(	Low	12 months	9	well controlled	well controlled	2	2	2	2	0	good	4 weeks	2	1	2	2	2	2	2	2	2	119	-1	127.5	-2.18	17.2	-1.81	19.7	-2.86
38	15	male	2	jodhpur	22/6/21	10.44	17.65	foracort 2(	Low	24 months	10	well controlled	well controlled	2	1	2	2	0	poor	8 weeks	2	1	1	2	2	2	2	2	2	157	0.34	168	0.44	47.3	0.36	47	-0.56
39	11	male	1	jodhpur	09-02-21	18.43		foracort 1(	low	12 months	5	well controlled	well controlled	2	2	2	2	0	good	7 weeks	2	1	2	1	2	2	2	2	2	128.5	-1.49	135	-0.99	22.8	-1.27	26	-1.31
40	11	male	2	jodhpur	09-02-21	19.49		foracort 1(	low	36 months	6	well controlled	well controlled	2	2	2	2	0	good	8 weeks	2	1	1	2	2	2	2	2	2	116	1.05	124	1.2	17	0.78	20.88	0.84
41	16	male	2	jodhpur	09-02-21	12.65	33.6	foracort 4(	medium	24 months	6	well controlled	well controlled	2	2	2	2	0	good	6 weeks	2	1	1	2	2	2	2	2	2	160.3	-0.4	165	-0.4	46	-0.45	49.9	-0.47
42	9	male	2	sangriya	23/9/21	7.277	22.465	foracort 4(	medium	5 months	3	well controlled	well controlled	2	2	2	2	0	good	7 weeks	2	1	1	2	2	2	2	2	2	118	0.54	118	0.55	16	0.67	18	0.77
43	15	male	1	jodhpur	22/3/21	5.96	25.04	budecort 1	low	9 months	6	Well controlled	well controlled	2	2	2	2	0	good	8 weeks	2	1	1	2	2	2	2	2	2	155	-0.46	159.5	-0.57	40	-0.86	43	-0.97
44	17	Female	2	Pali	01-11-21	8.65	19.76	Foracort 2	Low	24 months	9	Moderately controlled	well controlled	2	2	2	2	0	Good	5 weeks	2	1	2	2	2	2	2	2	2	148	0.67	154	1.23	36	0.45	39	0.45
45	10	Male	1	Jodhpur	01-11-21	17.43		Foracort 2	Low	24 months	10	Moderately controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	125	-1.27	129	-1.2	22	-1.56	28	-0.47
46	12	Male	1	Jodhpur	26-02-21	16.45		Foracort 1	Low	24 months	7	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2	132	0.42	145	-0.9	32	-0.42	37	-0.34
47	7	Female	2	Balesar	24-09-21	10.54	23.672	Foracort 2	Low	24 months	5	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	2	2	2	2	2	2	2	113	-0.73	115	-0.73	23	0.22	25	0.34
48	9	Male	2	Pali	24-09-21	17.04		Foracort 2	Low	12 months	5	Well controlled	well controlled	2	2	2	2	0	Poor	12 weeks	2	1	2	2	2	2	2	2	2	107	-0.98	115	-0.73	17	0.83	22	0.22
49	7	Female	2	Jhalawar	04-11-21	17.4		Foracort 2	Low	12 months	6	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2	122	1.39	128	1.24			26	0.99
50	14	female	1	Jodhpur	04-11-21	6.78	21.42	Foracort 4	Medium	12 months	8	Partly controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	150	-0.4	152	-0.36	50	0.65	52	0.56
51	15	Female	2	Jodhpur	04-11-21	4.22	25.45	FORACORT	HIGH	6 months	7	Well controlled	well controlled	1	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2	152	-0.16	155	-0.17			39	-1.13
52	13	Female	2	Jodhpur	04-11-21	9.45	21.86	Foracort 2	Low	12 months	8	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2	145	-1.34	153	0.86	38	0.54	42	0.82
53	8	Male	2	Jodhpur	04-11-21			Foracort 4	Medium	24 months	4	Well controlled	well controlled	1	2	2	2	0	Good	6 weeks	2	1	1	2	1	2	2	2	2	120	-0.98	124.5	-1.02	16	-1.04	23	-0.83
54	17	Male	2	Naggaur	10-11-21			Foracort 2	Low	12 months	6	Partly controlled	well controlled	1	2	2	2	0	Poor	8 weeks	2	1	1	2	2	2	2	2	2			174	0.13			61	0.42
55	9	Male	2	Jodhpur	11-11-21	16.27		Foracort 2	Low	12 months	7	Partly controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	126	-0.21	131	-0.06	20.4	-1.04	20.7	-1.48
56	6	Male	1	Jodhpur	11-11-21	8.32	22.4	Foracort4(	Medium	12 months	4	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	116		122	1.42	22	1.44	26	1.57
57	14	Male	2	Naggaur	06-11-21	6.56	35.64	Foracort 4	Medium	12 months	10	Well ontrolled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2			163	1.23			59	1.17
58	8	Female	2	Jodhpur	11-11-21	4.34	25.17	Budecort 3	Medium	24 months	6	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2	115	0.26	129	0.57	16.6	-0.71	22.4	-0.34
59	7	Male	1	Jodhpur	18-11-21	6.127	34.34	Foracort 4	Medium	6 months	6	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	124	0.31	125	0.32	22.3	-0.08	22	0.01
60	12	Female	1	Jodhpur	18-11-21	17.2		Foracort 2	Low	24 months	9	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	1	2	2	2	2	2	2			136	-1.73			34	-0.74
61	6	Male	1	jodhpur	21-10-21	6.45	23.5	Foracort 2	Low	12 months	5	Well controlled	well controlled	2	2	2	2	0	Good	6 WEEKS	2	1	1	2	2	2	2	2	2	110		112		20		21	-1.03
62	8	Female	2	Jodhpur	19-10-21	5.25	21.5	Foracort 2	Low	6 months	8	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	2	2	2	2	2	2	2	124	-0.89	129	-0.31	18	-1.69	21	-1.27
63	13	male	1	nagaur	19-10-21	6.094		Foracort 4	Medium	12monthe	10	Well controlled	well controlled	2	2	2	2	0	Good	7 weeks	2	1	1	2	2	2	2	2	2	143	-1.28	146	-1.05	30.5	-1.34	31.9	-1.32
64	7	Male	2	Jodhpur	11-10-21	6.57	35.76	Foracort 4	medium	12 months	3	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	2	2	2	2	2	2	2	121	0.41	122	0.23	18	-0.72	19.5	-0.69
65	11	Female	2	Keru		9.36	37.9	Foracort 2	Low	12 months	6	Partly controlled	well controlled	2	2	2	2	0	Poor	10 weeks	2	1	1	2	2	2	2	2	2			149.2	0.86			38.4	0.37
66	6	Male	1	Jodhpur	03-09-21	7.42	21.38	Budecort 4	Medium	12 months	5	Well controlled	well controlled	2	2	2	22	0	Good	7 weks	2	1	2	2	2	2	2	2	2	116	0.76	120	0.93	18	0.44	22	0.75
67	11	Male	2	Jodhpur		3.54	18.04	Foracort 4	Medium	24 months	5	Poorly controlled	poorly controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2			132	-1.48	24	-0.83	28	-0.96
68	7	female	2	Jodhpur		16.09		Foracort 2	Low	8 months	6	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	2	2	2	2	2	2	2			128	1.39			26	0.99
69	14	Female	2	Jodhpur		9.56	32.67	Foracort4(	Medium	18 months	13	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2			164.5	1.37			45	-0.15
70	17	Female	1	Jodhpur		5.55	21.73	Foracort 4	Medium	3 months	10	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	2	2	2	2	2	2	2				160	0.42		37.8	-1.71
71	12	Female	1	Jodhpur	12-06-21	4.43	24.19	Foracort 2	Low	18 months	10	Poorly controlled	poorly controlled	2	2	2	2	0	Poor	8 weeks	2	1	1	2	2	2	2	2	2			132	-2.27			38	-0.21
72	10	Male	2	Jodhpur		5.8	19.8	Foracort 6	High	12 months	6	Well controlled	well controlled	2	2	2	2	0	Good	4 weeks	2	1	1	2	2	2	2	2	2	137	0.1	138.5	0.12	24.5	-0.44	28	-0.47
73	14	Female	1	Jodhpur	02-12-21	5.59	22.19	Budecort 2	Low	24 months	7	Poorly controlled	poorly controlled	2	2	2	2	0	Poor	8 weeks	2	1	2	2	2	2	2	2	2			160	0.78			34.6	-1.48
74	13	Male	1	Jodhpur	02-12-21	3.27	24.75	Foracort 4	Medium	24 months	10	Well controlled	well controlled	2	2	2	2	0	Good	7 weeks	2	1	1	2	2	2	2	2	2	145.8	0.32	150	-0.54	29	-0.8	39	-0.44
75	17	Female	1	Jodhpur	02-12-21	12.56	40.42	Foracort 4	Medium	3 months	17	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	50	-0.13	50	-0.14	165	1.2	165	1.2
76	11	Male	1	Jodhpur	02-12-21	6.54	28.73	Foracort 4	Medium	36 months	9	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	2	2	2	2	2	2	2	24.2	-0.64	25	-0.64	137	-1.44	138	-1.5
77	12	Male	2	Jodhpur	02-12-21	4.11	29.32	Foracort 4	Medium	6 months	12	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2			137	-2.16		30.2	-1.59	32	-1.44
78	6	Male	1	Jodhpur	03-12-21	11.08		Budecort 4	Medium	12 months	5	Well controlled	well controlled	2	2	2	2	0	Good	7 weeks	2	1	1	2	2	2	2	2	2	20	1.22	24	1.21	116	0.67	119	1.05
79	7	Male	2	Barmer	06-12-21	7.54	23.3	Foracort 4	Medium	8 months	6	Well controlled	well controlled	2	2	2	2	0	Good	6 weeks	2	1	1	2	2	2	2	2	2	128	1.24	130	1.27	21	-0.25	24	-0.96
80	9	Female	1	Jodhpur	06-12-21	4.36	22.87	Budecort 2	Low	3 years	5	Poorly controlled	partly controlled	2	2	2	2	0	Good	8 weeks	2	1	2	2	2	2	2	2	2	134.5	0.39	134.5	0.39	22	-1.06	22	-1.06
81	14	Male	1	Jodhpur	12-12-21	17.54		Foracort 4	Medium	3 months	14	Well controlled	well controlled	2	2	2	2	0	Good	8 weeks	2	1	2	2	2	2	2	2	2								