Original Research Article

Effect of Budesonide Inhalation on Asthmatic Child: A Randomized Controlled Trial

Abstract

Background: Asthma is a heterogeneous inflammatory airway disease defined by a history of intermittent respiratory symptoms and inhaled steroids are the cornerstone of all guidelines on asthma treatment. The aim of this study was to compare the clinical control of inhaled BUD regimens for the treatment of preschool children with recurrent wheezing.

Methods: This prospective randomized controlled study was carried out on 70 pediatric patients aged from 6-12 years old, both sexes, with and the following criteria: having ≥ 4 wheezing episodes in the past year; and meeting at least 1 major criterion or at least 2 minor criteria. Patient selection was strictly controlled by doctors who specialize in the diagnosis and treatment of children's respiratory diseases, especially asthma. The included children had mild-to-moderate asthma.

Results: After treatment, FEV1, FVC and FEV1: FVC were significantly higher in group A compared to group B (P value <0.001). Urgent care visits due to asthma and Hospitalizations due to asthma were significantly lower in group A compared to group B (P value = 0.003 and 0.008 respectively).

Conclusions: We have shown that the Budesonide Inhalation is an effective and safe management for long term asthma treatment. Budesonide was also associated with a greater reduction in asthma symptoms with an increase in the number of episode free days as compared with placebo.

Keywords: Budesonide, Inhalation, Asthmatic Child, Corticosteroids, spirometry

Introduction:

Asthma is a heterogeneous inflammatory airway disease defined by a history of intermittent respiratory symptoms including wheeze and cough, and with variable expiratory airflow obstruction across all asthma severities [1]. The global prevalence of asthma has increased in the past 60 years; it is estimated that globally over 300 million people are living with asthma, including 11.6% of children aged 6–7 years [2].

Despite the availability of effective maintenance treatments, including inhaled corticosteroids (ICS), patients continue to suffer from periodic asthma worsening, and the incidence of exacerbations in both paediatric and adult patients remains high. All patients are at risk of preventable and potentially serious exacerbations, irrespective of asthma severity [3, 4].

Short-acting beta2-agonists (SABA), such as albuterol (salbutamol), are often used as rescue medication for symptom relief by patients with asthma of all severities. SABA induce airway smooth muscle relaxation and provide rapid symptom relief, but do not address the underlying airway inflammation. Patients may therefore continue to experience worsening of asthma and remain at risk of exacerbations, regardless of their maintenance therapy [5, 6].

Inhaled steroids (ICS) are the cornerstone of all guidelines on asthma treatment. They reduce symptoms in children with asthma, improve quality of life in asthmatic children and their families, decrease patients and their parents absence from school/work, reduce airway inflammation, and improve lung function, bronchial responsiveness and exercise-induced asthma [7, 8].

In older children, the admission and particularly readmission rates for acute asthma have decreased in these countries. The use of inhaled steroids has thus had a major impact upon daily life and the "mastering" of asthma in asthmatic children [9].

The Childhood Asthma Management Program was designed to evaluate whether continuous, long-term treatment (over a period of four to six years) with ICS (budesonide) safely produces an improvement in lung growth as compared with treatment for symptoms only (with albuterol and, if necessary, prednisone, administered as needed) [10, 11].

Budesonide, also treat the inflammation, and there is evidence of a 'window of opportunity' during periods of worsening symptoms, in which a timely administration of ICS can prevent the symptoms developing into an exacerbation [12].

The local side-effects of inhaled steroids on skin, the mucous membranes of the respiratory tract, and the oropharyngeal area are also well known, but have received much less attention than the systemic side effects. The local side-effects consist of perioral dermatitis, oral candidiasis, hoarseness, dysphonia, cough during inhalation and a feeling of thirst [13]. We aimed to compare the clinical control of inhaled BUD regimens for the treatment of preschool children with recurrent wheezing.

Patients and Methods:

This prospective randomized controlled study was carried out on 70 pediatric patients aged from 6-12 years old, both sexes, with and the following criteria; having ≥ 4 wheezing episodes in the past year; and meeting at least 1 major criterion or at least 2 minor criteria. The major criteria include parental history of asthma, physician-diagnosed atopic dermatitis, and allergic sensitization to at least 1 aeroallergen. The minor criteria include wheezing unrelated to colds, peripheral blood eosinophils ≥ 4%, and allergic sensitization to milk, eggs, or peanuts. (Patient selection was strictly controlled by doctors who specialize in the diagnosis and treatment of children's respiratory diseases, especially asthma).

The children had mild-to-moderate asthma, as defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma. The children's airway responsiveness to methacholine, as indicated by the

concentration of the drug that caused a 20 percent decrease in the FEV 1, was 12.5 mg per millilitre or less. They had no other clinically significant conditions. The children's parents or guardians signed an informed-consent form approved by the Ethical committee.

Exclusion criteria were having wheezing caused by organic lesions and mechanical factors; having received more than six systemic glucocorticoids; having used other asthma control drugs; and having guardians who did not know the child's medical history or did not agree to participate in the study.

Randomization:

Cases were randomly divided equally into two groups by sealed opaque envelopes and a computer-generated sequence. Group A: 35 Children were randomly assigned to receive budesonide (Pulmicort, AstraZeneca, Westborough, Mass.) (200 µg twice daily, delivered by two 100-µg actuations of a breathactuated metered-dose inhaler [Turbuhaler, AstraZeneca]), and group B (control group): 35 Children was assigned to receive a matching placebo.

The total daily doses of budesonide (400 µg) and nedocromil (16 mg) were administered as two equal daily doses to maximize adherence to the treatment regimen [14], Albuterol (Ventolin, Glaxo Wellcome, Research Triangle Park, N.C.), delivered by two 90-µg actuations of a pressurized metered-dose inhaler, was used as needed for symptoms of asthma or to prevent exercise-induced bronchospasm. Short courses of oral prednisone were prescribed for exacerbations of asthma. If control remained unsatisfactory, replacement or addition of medications was allowed. To account for remission, it was permissible to taper the study medication to a dose of zero (by stepwise reductions from 100 percent to 50 percent to zero), according to defined procedures. Algorithms guided the resumption of the full dose of the study medication [15].

Asthma control was defined as optimal when four of the following criteria were fulfilled:

(a) The child leads a normal life, including normal physical activity, (b) Use of rescue terbutaline < 1 per week, (c) Diurnal variation in PEF 110% on 2 5 days per week, (d) Asthma symptoms <once a week, (e) PEF and/or FEV, 2 100% of predicted normal, (I) < 10% fall in FEV, after a standardization exercise test (if performed). When control was optimal a reduction in budesonide dose was attempted.

Asthma control was considered as unacceptable when the criteria for acceptable control were not fulfilled.

In that case the budesonide dose was increased, or other treatment added.

If any of the following criteria: (a) A fall in morning PEF >20%, (b) Use of >5 inhalations of rescue terbutaline, (c) >one-step worsening in symptom score (i.e., from 0 to 2 or from 1 to 3).

Outcome Measures

Primary outcomes where spirometry was performed twice yearly, with measurements obtained both before and after the administration of a bronchodilator.

Secondary outcomes included the number of systemic corticosteroid courses (oral or intravenous), wheezing episodes, and urgent care visits for wheezing during the 52-week treatment period. Side effects of the drug.

Treatment failure indicated that the wheezing was not under continuous control, a wheezing attack was serious enough to require tracheal intubation, or serious adverse reactions related to the treatment drugs occurred during the follow-up period.

Statistical analysis:

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when

appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results:

In this study, 97 patients were assessed for eligibility, 18 patients did not meet the criteria and 9 patients refused to participate in the study. The remaining 70 patients were randomly allocated into 2 groups (35 patients in each). All allocated patients were followed-up and analyzed statistically. **Figure 1**

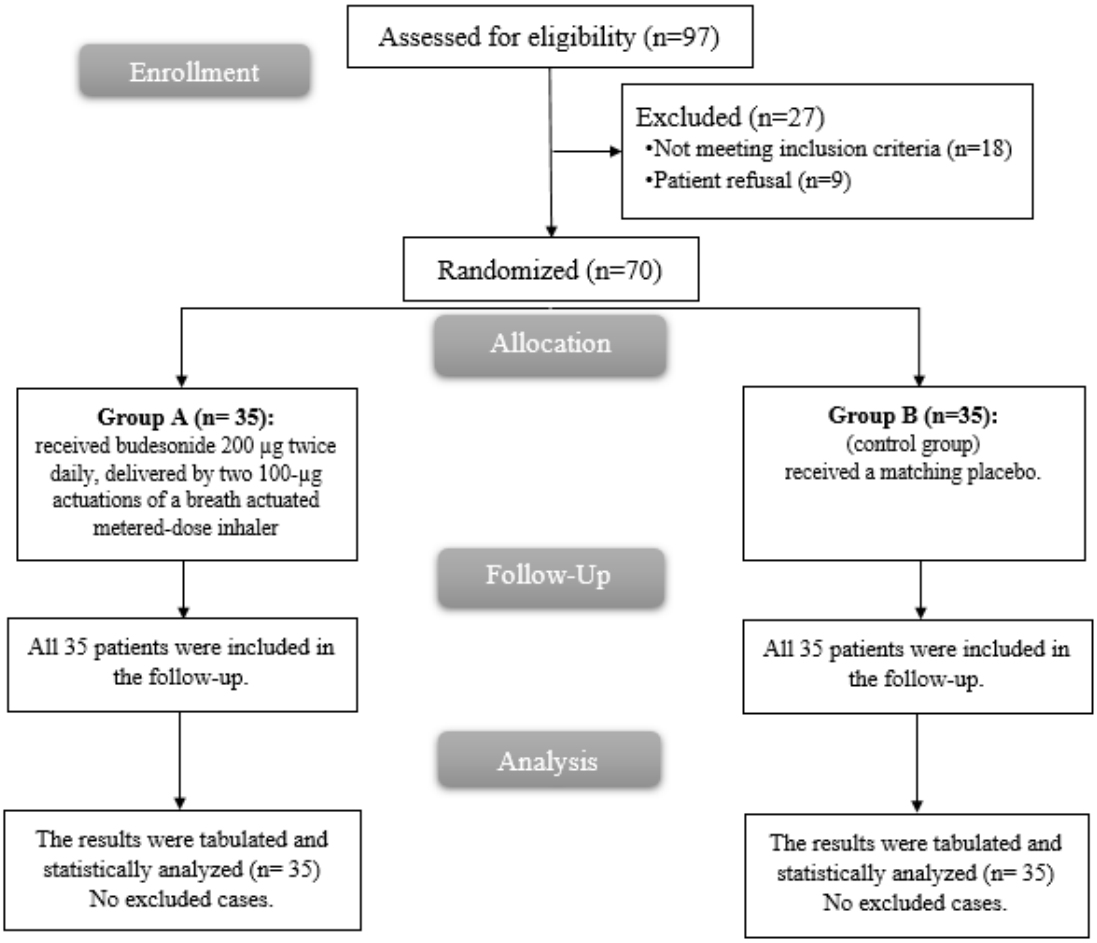

Figure 1: CONSORT flowcahat of the enrolled patients

Baseline characteristics (age, sex, weight, height, weight and BMI), age of onset of asthma, duration of asthma, time since diagnosis of asthma, severity of asthma, treatments in 6 months before enrolment, hospitalizations for asthma in year before enrolment and patients

who used systemic glucocorticoids over the past year were insignificantly different between both groups. **Table 1**

Table 1: Baseline characteristics of the studied patients

		Group A (n=35)	Group B (n=35)	P value
Age (years)		9.5 ± 1.84	8.8 ± 1.98	0.154
Sex	**Male**	31 (88.57%)	28 (80%)	0.324
	Female	4 (11.43%)	7 (20%)	
Weight (Kg)		41.09 ± 9.47	42.2 ± 9.94	0.633
Height (m)		1.45 ± 0.08	1.42 ± 0.07	0.081
BMI (Kg/m^2)		19.58 ± 4.63	21.05 ± 5.37	0.224
Age of onset of asthma (years)		4.34 ± 1.03	4.6 ± 1.09	0.313
Duration of asthma		1.38 ± 0.58	1.36 ± 0.61	0.904
Time since diagnosis of asthma (years)		6.74 ± 1.38	7.26 ± 1.42	0.129
Severity of asthma	**Mild**	18 (51.43%)	16 (45.71%)	0.632
	Moderate	17 (48.57%)	19 (54.29%)	
Treatments in 6 months before enrolment	**Cromolyn or nedocromil**	17 (48.57%)	11 (31.43%)	0.312
	Inhaled corticosteroid	11 (31.43%)	13 (37.14%)	
	Oral corticosteroid	7 (20%)	11 (31.43%)	
Hospitalizations for asthma in year before enrollment		10 (28.57%)	9 (25.71%)	0.788
Patients who used systemic glucocorticoids over the past year		24 (68.57%)	20 (57.14%)	0.332

BMI: body mass index, Data are presented as mean ± SD or frequency (%),

Risk factors (parent smoker, eczema, parental asthma, rhinitis, any aeroallergen sensitivity and food sensitivity) and laboratory markers were insignificantly different between both groups. **Table 2**

Table 2: Risk factors and laboratory markers in the studied patients

		Group A (n=35)	Group B (n=35)	P value
Parent smoker		19 (54.29%)	23 (65.71%)	0.329
Eczema		13 (37.14%)	11 (31.43%)	0.614
Parental asthma		22 (62.86%)	15 (42.86%)	0.097
Rhinitis		25 (71.43%)	20 (57.14%)	0.318
Any aeroallergen sensitivity		12 (34.29%)	10 (28.57%)	0.606
Food sensitivity		10 (28.57%)	14 (40%)	0.313
Laboratory markers	**High CRP**	22 (62.86%)	24 (68.57%)	0.714
	High eosinophil	32 (91.43%)	29 (82.86%)	0.284

CRP: C- reactive protein, Data are presented as mean ± SD or frequency (%),

Clinical symptoms (night wheezing, day wheezing, day cough and night cough) were insignificantly different between the studied groups. **Figure 2**

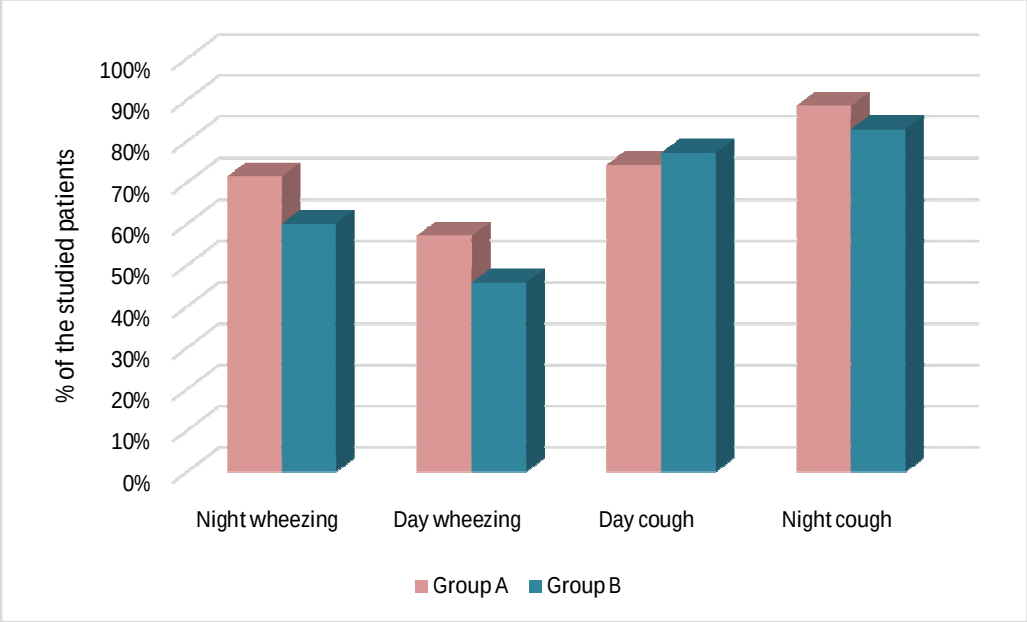

Figure 2: Symptoms between the studied patients

Baseline spirometric measures (FEV1, FVC and FEV1: FVC) were insignificantly different between both groups. After treatment, spirometric measures (FEV1, FVC and FEV1: FVC) were significantly higher in group A compared to group B (P value <0.001). **Table 3**

Table 3: Spirometric measures in the studied patients

		Group A (n=35)	Group B (n=35)	P value
Baseline	**FEV1 (%)**	77.77 ± 4.24	77.83 ± 5.06	0.959
	FVC	72.8 ± 4.19	72.77 ± 4.7	0.979
	FEV1: FVC	1.07 ± 0.08	1.04 ± 0.11	0.152
After treatment	**FEV1 (%)**	90.26±3.45	84.29±3.31	**<0.001***
	FVC	87.77±4.53	80.23±3.11	**<0.001***
	FEV1: FVC	1.06±0.06	1.02±0.06	**<0.001***

FEV1: forced expiratory volume in one second. FVC: forced vital capacity, Data are presented as mean ± SD or frequency (%), *: statistically significant as P value<0.05

Daily diary-card measures (Morning peak flow and Night awakenings) were insignificantly different between both groups. Regarding the morbidity during follow up, Urgent care visits due to asthma and Hospitalizations due to asthma were significantly lower in group A compared to group B (P value = 0.003 and 0.008 respectively) whereas fractures were insignificantly different between both groups. **Table 4**

Table 4: Changes in daily diary-card measures and morbidity during follow up of the studied patients

		Group A (n=35)	Group B (n=35)	P value
Daily diary-card measures	**Morning peak flow**	20 (57.14%)	20 (57.14%)	1.0
	Night awakenings	8 (22.86%)	14 (40%)	0.211
Morbidity	**Urgent care visits due to asthma**	7 (20%)	19 (54.29%)	**0.003***
	Hospitalizations due to asthma	5 (14.29%)	15 (42.86%)	**0.008***
	Fractures	14 (40%)	7 (20%)	0.067

Data are presented as mean ± SD or frequency (%), *: statistically significant as P value<0.05

Discussion:

Asthma is a disease of chronic airway inflammation characterized by reversible airway obstruction and increased airway responsiveness [16]. Recent studies have demonstrated that asthma can be associated with impaired lung growth during childhood and with a progressive decline in pulmonary function in adulthood [17, 18]. Clinical practice guidelines recommend anti-inflammatory medication for the long-term control of persistent asthma; treatment with inhaled corticosteroids or nedocromil is recommended for children [19].

This study included only children with mild to moderate asthma, The natural history of an asthma exacerbation might differ with both the severity of the underlying condition and the trigger of the exacerbation, and more information about this could be gained from a larger study involving a variety of children with asthma.

Result of pulmonary function

Our findings showed that budesonide improved lung function, as measured by the percentage of the predicted value for FEV1 after the administration of a bronchodilator, was unexpected. FEV 1 was chosen as the primary outcome measure because it is widely accepted as the most clinically useful and predictive measure of lung function. It is highly reproducible and correlates well with the progression of disease, use of health care, and severity of asthma and accurately describes the natural history of childhood asthma [20, 21]. The value after

bronchodilator use was chosen as the outcome measure because it minimizes the effects of airway constriction and has less variability over time in individual patients than the value before bronchodilator use. The use of budesonide was associated with improvement in the FEV 1 before bronchodilator use, when measured as a percentage of the predicted value [22].

FEV 1: FVC ratio before bronchodilator use decreased over time in both groups. The decrease was minimized by budesonide. Also, our findings revealed that the rates of hospitalization and of urgent care visits and the need for additional therapy and oral prednisone were lowest in the budesonide group.

In line with our results Szefler et al. [23] found that a benefit of budesonide in terms of lung function, as measured by the FEV1 after bronchodilator use, was evident at one year, but not at four years; a reduction in linear growth velocity in children treated with budesonide was evident at one year.

It was surprising that treatment induced increases in FEV, and FMEF was related to the interval

between the onset of asthma symptoms at the start of inhaled corticosteroid therapy. This effect of delayed treatment did not appear to be influenced by the previous treatment of the child. during run-in and control treatment suggest that sub optimally treated asthma may result in irreversible airway obstruction in children. Furthermore, it seems that treatment with inhaled treatment is started early after the debut of symptoms. This suggestion agrees well with the findings.

The use of a double dose of inhaled steroids administered for only three days was a compromise between common practice and safety considerations [24]. In New Zealand, it is most common for the dose of inhaled steroids to be doubled until the child's condition returns to normal [25]. However, during this study the children were potentially receiving placebo treatment for an exacerbation.

Allen et al. [26] evaluated 95 articles and included 21 studies involving 810 patients. Both oral and inhaled steroids were assessed, and it was concluded that a significant, though weak impairment was found for oral steroids, whereas inhaled beclomethasone dipropionate was not associated with growth impairment, but with attaining normal final stature. Our study had several limitations as single centre study with relatively small sample size.

Conclusion: We have shown that the Budesonide Inhalation is an effective and safe management for long term asthma treatment. Budesonide was also associated with a greater reduction in asthma symptoms with an increase in the number of episode free days as compared with placebo. Further studies are needed with different ages and with different doses and regimen of Budesonide.

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