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Research Article

Effectiveness of Nebulized Budesonide in the Treatment of Acute Asthma: A double-Blind Placebo-Controlled Trial

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ABSTRACT:

BACKGROUND:

Inhaled corticosteroids administered in high and repeated doses which effect simultaneously with bronchodilators is a way to maintain the effect throughout the time. The acute effects of nebulized budesonide as an emergency treatment of acute asthma in children have been evaluated in few clinical studies.

OBJECTIVE:

The analysis of the early clinical impact of adding repeated doses of nebulized budesonide in the treatment of acute asthma in the emergency setting on clinical respiratory score, Peak expiratory flow rates and hospital admission after 4 hours of treatment.

PATIENTS AND METHODS:

The study was a double-blind and placebo-controlled trial from April 2017 to January 2018 in children who attended the pediatric emergency unit at Children welfare teaching hospital due to an acute attack of asthma were evaluated. Clinical respiratory score and the peak expiratory flow rates were recorded in all patients at the start of the study by a pediatrician. Both groups received three consecutive doses of nebulized salbutamol (0.15 mg/kg/dose) and one dose of intravenous dexamethasone (0.15 mg/kg). During this treatment, for patients in group A the salbutamol nebulizer was mixed with normal saline while patients in group B three doses of nebulized budesonide (1mg/dose) which were combined with the nebulized salbutamol. Four hours later clinical respiratory scores and the peak expiratory flow rates were measured once more by the same blinded pediatrician.

RESULTS:

Respiratory rate showed significant difference between budesonide and placebo groups after 4 hours from the start of nebulizer therapy (P = 0.01). While others clinical respiratory scores variables like auscultation, accessory muscle, SPO2, color showed evident improvement after 4 hours but the differences were not statistically significant for each. The mean PEFR percent in budesonide group after 4 hours was (156±78.1) and that of placebo group was (119±37.9). Although the differences in PEFR between two groups was evident, it did not reach statistical significance (P= 0.3).

CONCLUSION:

The effectiveness of nebulized budesonide in addition to systemic steroids and nebulized salbutamol in early treatment of moderate asthmatic attacks in children 2-15 years of age in emergency setting clinically provided meaningful benefits in improving the clinical respiratory scores and PEFR and decreasing admission to the ward.

KEYWORDS: budesonide, asthma, inhaled corticosteroids, children, emergency.

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INTRODUCTION:

Asthma is a persistent inflammatory state of reversible airway blocking. Exacerbation, which tends to be a transient deterioration of symptoms, is part of the disease's evolutionary course, which can be a result in failure in continuing long-term treatment.

They also lead to long-term emergency presentations, hospitalization and complications [(1)].
This places enormous pressure on the family and the community, and contributes for several missing school days, and may rob the child of both social contact and educational attainment. Childhood asthma burdens health services due to medical and hospital appointments and medical expenses[(2)].
It has been reported that in a number of countries with influential regional differences, asthma in childhood has significantly risen over the last 30 years. The reasons are still difficult to ascertain for this substantial rise and are likely to include multiple factors[1]. Varying exposures to respiratory conditions, indoor and/or outdoor pollutants, and diet can influence these variations[2]. These variations may also be contributed by genetics, lifestyles and environmental factors[(3)].
Asthma affects about 14 per cent of boys and 10 per cent of girls during childhood. In children under the age of 18 years, the prevalence of asthma (described as asthma over the past year) increased from 3.6 per cent in 1980 to 9.3 per cent in 2010[(4)].
Whilst there have been racial differences in negative asthma outcome, such as mortality and morbidity, since the eighties of the last century, racial differences in prevalence have only recently doubled in black as compared to white children in 2011, in comparison with a little difference to no in the 1980s[(5)].
Asthma is not a rare problem in Iraq, especially in primary school children. Unfortunately, despite the increased burden of this health issue during our clinical work, no national database could be obtained[(6)].
Genetics, parental smoking, diet and nutrition, psychological stress, lung infection, antibiotic use, social background, allergic sensitization, child age, presence of animals in the home, skin problems, gastrointestinal problems, food allergy and maternal education were significantly related to, and were the main risk factors for childhood asthma[(7,8)].
Asthmatic airways have two main pathological components, inflammation, and hyper-reactivity[9]. Inflammatory changes in airways include increased secretions of airway mucus, airway wall edema, inflammatory cell infiltration, epithelial cell injury, smooth muscle hypertrophy and submuscular fibrosis[10]. Cell infiltration consists primarily of eosinophils, neutrophils, lymphocytes, basophils, mast cells and macrophages. The proportion of these cells can differ significantly between patients, showing asthma diversity[(11)].
A viral infection of the respiratory tract is by far the major cause of acute asthma exacerbation in children in up to 80 per cent of cases[(12)]. Many viruses may exacerbate symptoms of asthma; rhinovirus is the most common[(13)]. Respiratory syncytial virus and influenza virus may also induce exacerbations[(14)]. Bacteria such as Hemophilus influenzae Moraxella catarrhalis and atypical bacteria have also been correlated with severe wheezing in children[(15)].
The incidence of exacerbations varies greatly depending on the nature of the attack, the degree of compliance with the prophylactic drugs and the cause of exposure[(16)]. Various multicenter surveys show that the admission rate for all emergency room (ER) attendants with acute asthma is 7-23%, with hospitalization needed for acute asthma exacerbation[(17,18)].
Patients with acute asthma may have elevated respiratory rate (RR), use of accessory respiratory muscles, wheezing and decreased oxygen saturation on pulse oximetry and, in more severe situations, speech difficulty, cyanosis, silent chest and alterations in mental state[(19)]. Based on a group of clinical findings as can be seen in (Table 1), exacerbations may be categorized as mild, moderate, or severe.

Table 1: General asthma severity rating[19]

Clinical finding	Severity grading		
	Mild	Moderate	Severe
Oxygen saturation %	≥95	90-94	<90
Peak expiratory flow rate (PEFR) %	≥70	40-69	<40
State of consciousness	Anxious	Agitated	Confused
Use of accessory respiratory muscles	No	Uncommon	Common
Speech	Sentences	Phrases	Words

Inhaled β2-agonists such as albuterol (salbutamol) are generally suitable in patients with mild asthma exacerbation to alleviate symptoms that may be repeated three times each 15 to 20 min, without the need for systemic corticosteroids[19].

On the other hand, in moderate exacerbation, additional doses of inhaled or nebulized β2-agonists could be administered every 30-60 min during the next 2-3 hours in addition to systemic corticosteroids at a dose of 2 mg / kg equivalent prednisolone up to 80 mg at an early stage of management, taking at least four hours to start working[20].

Systemic corticosteroids have been shown to increase symptom recovery, decrease admission rate and decrease relapse risk if administered three to five days post-exacerbation[21].

In case of severe attack of asthma, a high dose of inhaled or nebulized β2-agonist (8-12 puff) must be administered at least 1 hour every 15-20 min and may be administered repeatedly for up to four hours as mandated. The effectiveness of continuous versus intermittent nebulization of β2-agonist is a matter of debate[21]. Continuous nebulization should be given in the first hour, followed by intermittent nebulization if needed. It has been shown that ipratropium bromide decreases hospitalization rats. Hospital admissions and causality stay are significantly reduced by using nebulized ipratropium bromide in patients with moderate to severe asthma exacerbation in multiple clinical trials[22]. Magnesium sulfate and helio-oxygen (heliox) also may be considered in severe and unresponsive cases as alternative therapeutic modalities[23]. In children, oxygen therapy should be used to keep oxygen saturation of 95% or more[24].

Patients who improve clinically would be sent home following one hour of evaluation without further management. They will, however, have a change in their preventive treatment to avoid deterioration. Patients if not responding well to treatment for four hours should be admitted for more care[24].

To evaluate the clinical efficacy of repeated doses of nebulized budesonide in management of acute asthma of moderate severity and to measure the impact of adding nebulized budesonide in the emergency room (ER) setting on clinical respiratory score (CRS), peak expiratory flow rate (PEFR) and hospital admission after 4 hours of treatment.

PATIENTS AND METHODS:

From April 2017 to January 2018 twenty-six children who were admitted for moderate exacerbation of asthma to ER in Children Welfare Teaching Hospital (CWTH) / Medical City Complex / Baghdad were evaluated for the study. We include all patients following the Global Asthma Initiative (GINA) concept of asthma, which is "a heterogeneous condition, typically characterized by chronic airway inflammation. It is defined by history of respiratory symptoms such as wheeze, shortness of breath, tightness of the chest, and coughing. These symptoms vary with time and severity, along with variable airflow obstruction" and they have at least three attacks of shortness of breath and wheeze before and diagnosed by a pediatrician and showed an apparent response to bronchodilator. Physical examination and Clinical Respiratory Score (CRS) were conducted for the patient by a clinician. Children with moderately severe asthmatic episode ((Clinical Respiratory Score (CRS) = 4-7) was included in the study.

- Inclusion criteria were:
  a) Age from 2 years to15 years old.
  b) Having a (CRS) 4-7.
- Exclusion criteria: children who received nebulizer and steroid before arrived the hospital.

The study was approved by the ethical committee of CWTH, and a written consent was signed by the parents of the involved participants after detailed description of the study process.

Study Design:

A double-blind placebo-controlled study was designed. The participants matching the aforementioned criteria have been entered in a double-blind, randomized manner, in one of two categories, following the registration of the patient variables, (gender, age, current asthma and previous family background and medications). Physical signs were evaluated by the Clinical Respiratory Score system[25].

The respiratory rate, air entry, and presence of added sounds by auscultation, mental status, room air SpO2 and skin color were evaluated in this system as shown in Table 2. PEFR was estimated using OMRON peak flow meter; Model PFM20; Omron health care Europe B.V. krisweg 577, NL-2132 NA Hoofddorp. The best of three successful maneuvers was accepted.

Since a blinded doctor documented CRS (and PEFR in children over 5 years of age) for all

patients at the start of the test, both groups obtained three successive doses of nebulized salbutamol (0.15 mg / kg / dose) and one dose of intravenous dexamethasone (0.15 mg / kg). During this treatment, patients in group A the salbutamol nebulizer was mixed with normal saline while patients in group B three doses of nebulized budesonide (1mg/dose) which were combined with the nebulized salbutamol. Four hours later CRS and PEFR were documented once more by the same doctor.

Statistical Analysis:

All patient records were filled through computerized statistical software; version 20 of the Statistical Social Science Package (SPSS) has been used. Descriptive figures provided as (mean ± standard deviation) and frequency as percentages. Different contingency tables and relevant statistical analyses conducted, Chi – square used for categorical variables (Fishers exact test was used when the predicted variables were less than 5) and Mann – Whitney U (nonparametric) were used to compare the two means. Paired t-test compared to two consecutive events. For all statistical analysis, the significance value (P value) set at 0.05 and the outcome as tables and/or graphs. The statistical analysis of the study was carried out by a community medicine specialist.

Table 2: Clinical Respiratory Score (CRS)[25].

● Mild 1-3 ● Moderate = 4-7 ● Severe = 8-12

Variable		Score		
		0	1	2
RR	<2 months	<50	50-60	>60
	2-12 months	<40	40-50	>50
	1-5 years	<30	30-40	>40
	>5 years	<20	20-30	>30
Auscultation		Good air entry, scattered expiratory wheezing.	Decreased air entry, inspiratory and expiratory wheezes.	Absent breath sounds, severe wheezing, or markedly prolonged expiration
Accessory Muscles Use		Mild to no retractions OR nasal flaring on inspiration	Intercostal retractions.	substernal and suprasternal retractions.
Mental Status		Normal	Irritable	Lethargic
O_2 saturation		> 95%	90-95%	<90%
Color		Normal	Pale.	Cyanotic.

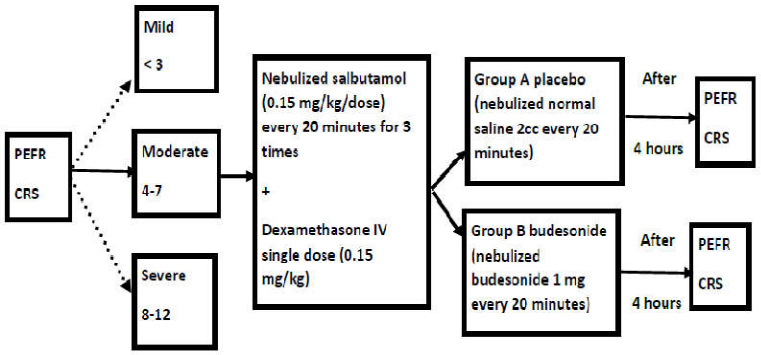

Figure 1: Study design.

RESULTS:

The study enrolled 26 children aged 2-15 years, admitted to ER with moderate asthmatic exacerbations. They were divided in to 2 groups according to type of nebulizer solution received. Budesonide group constituted of 12 children 10 males (83.33%),2 females (16.66%) and placebo group constituted 14 children 10 males (71.42%), 4 females (28.57%). No significant differences were detected between both groups regarding to age, sex and B.M.I as shown in (Table 3).

Table 3: Demographic features of the study groups

Variable	Budesonide		Placebo		P	Variable	Budesonide		Placebo		P
	No.	%	No.	%			No.	%	No.	%	
Age						B.M.I.					
2-5years	3	25.0	7	50.0	0.1* NS	Under weight	2	16.7	2	14.3	0.7* NS
5-9 years	4	33.3	6	42.9		Normal	3	25.0	6	42.8	
10-15 years	5	41.7	1	7.1		Over weight	4	33.3	4	28.6	
Gender						Obese	3	25.5	2	14.3	
Male	10	83.3	10	71.4	0.4* NS						
Female	2	16.7	4	28.6							

**NS: - not significant*

Four (33.33%) of budesonide group and 6 (42.9%) of placebo groups was partly controlled, while 8 children (66.7%) of budesonide group and 8 children (57.14%) of the placebo group was uncontrolled according to GINA guidelines of asthma control status. Statistically, there were no significant differences between both groups (P. value 0.2) as demonstrated in (Table 4).

Table 4: Distribution of control status of study groups by history.

Variable	Budesonide		Placebo		P
	No.	%	No.	%	
ICS use					
Yes	3	25.0	5	35.7	
No	9	75.0	9	64.3	0.5* NS
LTRA use					
Yes	7	58.3	9	64.28	
No	5	41.6	5	35.71	0.8*NS
Control status					
Partially	4	33.33	6	42.85	0.2*NS
Uncontrolled	8	66.66	8	57.14	

**NS: - not significant*

There was a marked association between positive family history of asthma and children treated with budesonide (p=0.004). All these findings were shown in (Table 5). There were no notable differences between children treated with budesonide or those treated with placebo in eczema history., allergic rhinitis, food allergy, drugs allergy, bronchiolitis, previous hospitalization to ER, previous hospitalization to wards and previous hospitalization to RCU. As seen in (Table 5).

Table 5: Distribution of children through past medical history of study groups.

Variable	Budesonide		Placebo		P	Variable	Budesonide		Placebo		P
	No.	%	No.	%			No.	%	No.	%	
History of eczema					0.1* NS	Previous hospitalization / ER					-
Yes	0	-	2	14.3		Yes	12	100.0	14	100.0	
No	12	100.0	12	85.7		No	0	-	0	-	
Allergic rhinitis					0.7* NS	Previous hospitalization / Ward					0.4* NS
Yes	5	41.7	5	35.7		Yes	8	66.7	11	78.6	
No	7	58.3	9	64.3		No	4	33.3	3	21.4	
Food allergy					0.3* NS	Previous hospitalization / PICU					0.1* NS
Yes	0	-	1	7.1		Yes	2	16.7	0	-	
No	12	100.0	13	92.9		No	10	83.3	14	100.0	
Drug allergy					0.1* NS	Family history of asthma					0.004** S
Yes	1	8.3	4	28.6		Yes	12	100.0	7	50.0	
No	11	91.7	10	71.4		No	0	-	7	50.0	
Bronchiolitis					0.09* NS						
Yes	11	91.7	9	64.3							
No	1	8.3	5	35.7							

**NS: - not significant, ** S: significant*

All included asthmatic children were of moderately severe asthmatic attacks with a mean clinical respiratory score of 4.83±0.93 for budesonide group and 5.14±1.29 for placebo group with no significant differences between the two groups at admission P. value (0.4), and no significant differences regarding the use of ICS (P. value=0.5) and LTRA (P. value=0.8) between the budesonide group and placebo group. All categories of CRS were recoded before and after nebulized therapy in both groups and the result in R.R showed significant differences between budesonide and placebo groups after 4 hours from the start of nebulizer therapy (P value 0.01). While other CRS variables like auscultation, use of accessory muscle, SPO2 and color showed remarkable improvement after 4 hours. However, statistically the differences were not significant to any group. The mean CRS of asthmatic children who received budesonide nebulizer after 4 hours was 1.98±0.99 after being 4.58±0.99 at admission. The mean CRS in placebo group after 4 hours was 2.28±1.06 after being 5.14 ±1.29 at admission. The differences in CRS of children were higher in the budesonide group than placebo group but the differences were statistically not significant (0.09) as shown in (Table 6). The means PEFR percent in budesonide group after 4 hours was (156±78.1) and that of placebo group was (119±37.9). Although the difference in PEFR between two groups was evident but did not reach statistical significance (P. Value 0.3) as shown in (Table 6). No significant differences were observed between children treated with budesonide and those treated with placebo regarding on clinical respiratory score on admission and clinical respiratory score after 4 hours. The difference between the two groups was significant regarding RR score 4hrs after nebulizer treatment (p=0.01), the RR score was higher among placebo group children. All these findings were shown in (Table 6).

Table 6: CRS and PEFR scores on admission and 4 hrs. after nebulizer therapy of study groups.

Scores	Budesonide	Placebo	P
	Mean±SD	Mean±SD	
RR on admission	1.66±0.49	1.85±0.36	0.2 *NS
RR 4hrs after nebulizer	0.66±0.49	1.0±0.001	0.01 **S
Auscultation on admission	1.16±0.38	1.0±0.001	0.1 *NS
Auscultation 4hrs after nebulizer	0.5±0.52	0.71±0.64	0.2 *NS
Accessory on admission	1.08±0.28	1.35±0.49	0.1 *NS
Accessory 4hrs after nebulizer	0.33±0.49	0.5±0.51	0.4 *NS
SPO_2 on admission	0.75±0.62	0.85±0.86	0.7 *NS
SPO_2 4hrs after nebulizer	0.08±0.28	0.14±0.36	0.6 *NS
Color on admission	0.08±0.28	0.07±0.26	0.9 *NS
Color 4hrs after nebulizer	0.00	0.00	-
CRS on admission	4.83±0.93	5.14±1.29	0.4 *NS
CRS 4hrs after nebulizer	1.58±0.99	2.28±1.06	0.09 *NS
PEFR (L/min) on admission	106.11±66.8	82±32.9	0.4 *NS
PEFR (L/min) 4hrs after nebulizer	156.6±78.9	119±37.9	0.3 *NS
PEFR (% of normal) on admission	38.16±18.75	40.15±17.30	0.94 *NS
PEFR (% of normal) 4hrs after nebulizer	57.67 ±20.81	55.66±20.45	0.86 *NS
Mental status	0	0	-

**NS: - not significant, ** S: significant*

The mean CRS of group A (Placebo) children on admission was 5.1±1.2 which significantly decreased 4hrs after nebulizer treatment to 2.28±1.06 (P<0.001). The mean CRS of group B (Budesonide) children on admission was 4.8±0.93 which significantly decreased 4hrs after nebulizer treatment to 1.58±0.99 (P<0.001). However, there was no significant difference between two study groups in mean CRS 4hrs after nebulizer (P=0.09). All these findings were shown in (Table 7).

Table 7: Distribution of CRS before and after nebulizer treatment of study groups

CRS	On admission	4hrs after nebulizer	P
	Mean±SD	Mean±SD	
Budeson	4.8±0.93	1.58±0.99	<0.001 **S
Placebo	5.1±1.2	2.28±1.06	<0.001 **S

** S: significant

The study shows 23 patients were discharged after 4 hours from ER and 3 were admitted to the ward, one of them belongs to the budesonide group and two patients belong to the placebo group but the difference did not show statistical significance.

DISCUSSION:

Using systemic steroids is effective in treating acute moderate and severe asthma exacerbations and are suggested by various asthma protocols like GINA and EPR3[26], and may decrease the need for hospital admission, but many children still need hospitalization[27]. Concerning the impact on exacerbation following discharge from ER, the majority of studies found reduced relapse rate with systemic corticosteroids[26]. Nevertheless, there was no extra advantage to courses longer than five days[28]. Nebulization is the recommended inhalation treatment for acute asthma attacks,

particularly for younger children. Budesonide solution is children's only FDA-approved nebulized inhaled corticosteroid. The effectiveness of nebulized budesonide in the management of acute exacerbation of asthma has been reported in a comparatively limited number of double-blind, placebo-controlled studies[29,30]. Budesonide's effects are rapid owing to its instantaneous anti-inflammatory activity which can have an additional benefit when employed as an alternative to systemic steroids in emergency department environments[31]. Substantial improvement was observed 4 hours after beginning nebulized budesonide in RR, Retractions, Auscultation and SPO2 percentage and overall Clinical Respiratory Scores but variations were statistically not significant except for RR. The outcome is in agreement with Y. Nuhogiu et al investigated 25 asthmatic children aged 5-15 years in a double-blind, placebo-controlled study similar to this study except for the use of parenteral methylprednisolone (1 mg / kg / dose, intramuscular) instead of intravenous dexamethasone (0.15 mg / kg). In the Y. Nuhogiu et al study the PEFR increments were statistically different in the two groups and there was no substantial difference in clinical pulmonary scores[32]. A remarkable improvement in PEFR (L / min) was also noted in our study, but the difference was not statistically significant. The impact of using inhaled budesonide with nebulized salbutamol was tested in another study conducted by Singhi et al in 60 asthmatic children aged 3-12 years with moderate asthmatic attacks. In the Singhi et al study, all subjects received nebulized salbutamol (0.15 mg / kg diluted with 3 ml normal saline) and were randomly assigned to receive either budesonide (400 mcg) or placebo inhalation for three doses at 30 minutes intervals of time. Researchers stated that children in budesonide group exhibited improved PEFR scores. Similar to our results it indicates the potential effect of the inhaled budesonide on salbutamol in children by increasing PEFR scores[33]. The absolute values of PEFR (L / min) were higher in the budesonide group after 4 hours of nebulizer therapy as seen in table-6. While the age ranges between budesonide and placebo were not statistically relevant as seen in table-3, older children were more frequent in the budesonide group. To prevent the non-randomized age variance influence on analysis; the PEFR (percentage of normal) for each observed child was also evaluated and revealed a higher percentage of PEFR (percentage of normal) in the budesonide group than the placebo group, however the discrepancy is less in magnitude and not statistically relevant. The main limitation of this study is the small sample size; therefore further researches with larger sample are required.

CONCLUSION:

The additive effects of nebulized budesonide to nebulized salbutamol and systemic steroids early in the treatment of moderate asthmatic attacks in children aged 2-15 years in ER setting is remarkable in improving the CRS and PEFR and admission to the ward. The study results recommend adding high repeated doses of nebulized budesonide to nebulized salbutamol and systemic steroids early in the treatment of moderate asthmatic attacks in children aged 2-15 years in ER setting to improve clinical condition and decrease the need for hospitalization. A larger study on longer period is recommended. It might achieve more significant results.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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