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ORAL PREDNISONE IS MORE EFFECTIVE THAN INHALED FLUTICASONE FOR PEDIATRIC SEVERE ACUTE BRONCHIAL ASTHMA

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ABSTRACT

Background: 5–25% of patient's relapse, needing admission for therapy of consecutive attacks**.** Inhaled corticosteroids are considered potent in the management of pediatric bronchial asthma. Inhaled corticosteroids vs. oral corticosteroids efficiency regarding the control of severe acute pediatric bronchial asthma is debatable. **Aim:** To assess the management potency of inhaled fluticasone and of oral prednisone during four hours following receiving in pediatric severe acute bronchial asthma. **Methods:** Our prospective, randomized and double-blind investigation included 115 patients, aged 6-14 years, of both sexes and with severe acute bronchial asthma (confirmed by a reference forced expiratory volume in one second of less than 60% of the predicted) at Queen Rania hospital, KHMC, Amman, JORDAN, during the period Jun 2021-Apr 2022. All patients were managed with bronchodilators and were administered one dose of 2 mg of inhaled fluticasone via an inhaler (Group I, n=58) or one dose of 2 mg of oral prednisone syrup per kilogram (Group II, n=57). Patients were evaluated each hour during the following 6 hours of receiving. Patients were sent home where the fluticasone group were administered 500 mcg of fluticasone twice daily by inhaler for one week and the prednisone group were administered 1 mg of oral prednisone per kilogram daily for one week. The modification in FEV1 as a percentage of the predicted from reference (time 0) to 6 hours was the primary outcome. Secondary outcomes were the modifications in the forced vital capacity (FVC) and the predicted peak expiratory flow rate as percentages of the predicted, the respiratory rate and oxygen saturation on room air. Lung-functions were performed in terms of the American Thoracic Society. The highest value was taken for investigation. These outcomes were recorded at half an hour prior to the primary nebulized dose of investigation drugs; at 0 minutes (prior to investigation drugs); at 1h, 2h, 6h and on day 8. Student's t-test was used for continuous parameters and Wilcoxon rank-sum test was used for skewed parameters. **Results:** The average reference forced expiratory volume in one second (percentage of predicted) was 44.3±10.2 in group I and 41.7±7.6 in group II. Eighteen patients (31.03%) managed with inhaled fluticasone and 6 patients (10.5%) managed with oral prednisone ($P<0.02$) were admitted. In the prednisone group, 15 of the 57 patients (26.3%) experienced an excellent reaction and 6 of 58 patients (10.3%) experienced an excellent reaction in the inhaled fluticasone. **Conclusions:** Patients with severe acute bronchial asthma must be managed with oral prednisone and not with inhaled fluticasone.

KEYWORDS: Bronchial asthma: severe; agents: oral prednisone, inhaled fluticasone; forced expiratory volume in one second.

INTRODUCTION

Acute severe bronchial asthma is considered the main frequent medical pediatric urgency. Optimum oxygenation, usual administration of aerosolized β2-adrenergic agonists, anticholinergic agents and systemic corticosteroids are the corner stone of management for severe bronchial asthma.[1] Systemic corticosteroids could reduce admission percentage in subjects with pediatric acute severe bronchial asthma[2], but not in all setups.[3] Oral corticosteroids reduce admission during four hours following urgent management in children[4] and avoid the development of clinical features.

The safety of repeated systemic corticosteroids is debatable.[5] Children are administered inhaled corticosteroids within acute attacks of asthma.1.5 mg of nebulized dexamethasone per kilogram was comparable in potency to 2 mg of oral prednisone per kilogram during four hours following receiving in urgent pediatric severe asthma.[6] Nebulized dexamethasone has systemic actions.[6] Inhaled flunisolide was more efficient to placebo for severe acute asthma.[7] mild asthma[8] or subacute asthma[9] in adults. Fluticasone propionate is a highly effective inhaled corticosteroid with an oral bioavailability of less than 1%[10] and twice the

efficiency of beclomethasone dipropionate in the management of chronic asthma.[11] Fluticasone propionate has less systemic actions than beclomethasone in similar doses.[12]

The objective of this investigation was to assess the management potency of inhaled fluticasone and of oral prednisone during four hours following receiving in pediatric severe acute bronchial asthma.

METHODS

Our prospective, randomized and double-blind investigation included 115 patients, aged 6-14 years, of both sexes and with severe acute bronchial asthma (confirmed by a reference forced expiratory volume in one second of less than 60% of the predicted) at Queen Rania hospital, KHMC, Amman, JORDAN, during the period Jun 2021-Apr 2022, after obtaining approval from our local ethical and research board review committee of the Jordanian Royal medical services and parents written informed consent. Patients with first wheezing attacks who had not been administered bronchodilator, who received oral prednisone during previous one week and receiving 1000 mcg of inhaled beclomethasone dipropionate or budesonide per day or 500 mcg of inhaled fluticasone per day were ruled out.

All patients were managed with bronchodilators and were administered one dose of 2 mg of inhaled fluticasone via an inhaler (Group I, n=58) or 2 mg of oral prednisone syrup per kilogram (maximum 60 mg) (Group II, n=57). Patients were evaluated each hour during 6 hours. 0.15 mg of nebulized albuterol per kilogram was given with an oxygen flow of 6-7 liters per minute during half an hour (prior), at reference (following) and half an hour, 1h, 2h and 3h (following) our investigation agents. Ipratropium bromide 250 mcg was given with albuterol.

Following the 6-hour interval, patients were sent home to keep on fluticasone or prednisone based on their random inclusion. The fluticasone group were administered 500 mcg of fluticasone twice daily by inhaler for one week and the prednisone group were administered 1 mg of oral prednisone per kilogram daily (maximum 40 mg daily) for one week. Albuterol was given to all participants via an inhaler (0.3 puff per kilogram per dose [100 mcg per puff; maximum 8 puffs per dose]) four times daily for one week.[13] On day 8, evaluation was mandatory. The first dose of nebulized albuterol and ipratropium was given instantly prior the investigation drugs which included eight puffs of fluticasone with 250 mcg per puff. A deep-inhalation with five seconds of breath-holding was commenced.[14]

The modification in FEV1 as a percentage of the predicted from reference (time 0) to 6 hours was the primary outcome. Secondary outcomes were the modifications in the forced vital capacity (FVC) and the predicted peak expiratory flow rate as percentages of the predicted, the respiratory rate and oxygen saturation on room air. Lung-functions were performed in terms of the American Thoracic Society [15]. The highest value was taken for investigation. These outcomes were recorded at half an hour prior to the primary nebulized dose of investigation drugs; at 0 minutes (prior to investigation drugs); at 1h, 2h, 3h and 6h and on day 8.

Statistics

Student's t-test was used for continuous parameters and Wilcoxon rank-sum test was used for skewed parameters. Fisher's exact test was used for binary parameters. The modification in lung-functions during time was investigated by mixed regression.

RESULTS

There were no remarkable characteristical discrepancies between both groups, but for gender (Table I). The enhancements in FEV1, FVC and predicted peak expiratory flow rate from reference (time 0) to 6h were remarkably more in the prednisone group than in the fluticasone group (Table II). The average reference forced expiratory volume in one second (percentage of predicted) was 44.3±10.2 in group I and 41.7±7.6 in group II. The FEV1 increased by an average of 9.2±10.2 percentage points in the fluticasone group and by 18.7±7.5 percentage points in the prednisone group six hours following management ($P<0.002$). The discrepancy in the modification in the FEV1 as a percentage of the predicted value from half an hour to 6h was remarkable ($P<0.002$). The enhancement in lung functions became slower following 2 hours. There was a gradual enhancement in FEV1 as a percentage of the predicted value in the prednisone group, but in the fluticasone group no enhancement happened following three hours.

In the prednisone group, 15 of the 57 patients (26.3%) experienced an excellent reaction, 37 patients (64.9%t) experienced a moderate reaction and 5patients (8.8 %) experienced a poor reaction. In the fluticasone group, 6 of 58 patients (10.3%) experienced an excellent reaction and 18 patients (31.03%) experienced a poor reaction ($P<0.002$). No patient in the prednisone group experienced a decrease in FEV1 from reference to 6 hours, but 24.1% of patients in fluticasone group did ($P<0.003$).

Between the 45 patients who were seen on day 8, the FEV1 as a percentage of the predicted value enhanced for the 15 patients in the fluticasone group and for the 30 patients in the prednisone group. The admission was more in the fluticasone group (31.03%) than in the prednisone group (10.5%). $P<0.01$. (Table III). Six of the discharged 40 children in the fluticasone group and 3 of the discharged 51 children in the prednisone group received oral corticosteroids.

Table I: Features of patients.

	GI	GII
Agent used	Inhaled fluticasone	Oral prednisone
No.(%)	58	57
Age (yrs.)average(SD)	8.1(2.2)	8.2(2.1)
Gender (NO., %) M **F**	28 30	38 19
Lung function tests (average, SD) % of predicted **FEV1 at half an hour.** **FEV1 at 0 min.** **FVC at 0 min.** **PEFR at 0 min.**	 33.6(6.2) 44.1(10.2) 48.4(13.6) 42.8(12.8)	 32.2(7.5) 41.7(7.6) 45.4(10.3) 38.5(10.9)
O2 Sat. at 0 min.(%) average(SD)	94.2(1.1)	94.1(1.4)
Resp. rate/min. at 0 min. average(SD)	30.5(6.1)	28.4(5.4)

Table II. Outcomes during 6 Hours post management.

outcome	**GI**		**GII**		**P**
	reference	**6h**	**reference**	**6h**	
FEV1(average, SD)	44.3(10.2)	53.5(14.1)	41.7(7.6)	60.4(10.8)	<0.002
FVC	48.4(13.6)	57.4(15.5)	45.4(10.3)	64.0(12.8)	0.005
PEFR	42.8(12.8)	50.4(16.4)	38.5(10.9)	58.4(14.8)	<0.003
RR/min	30.5(6.1)	28.4(5.4)	28.5(5.3)	26.4(4.2)	0.75
SpO2(%)	94.2(1.1)	94.1(1.4)	94.3(1.5)	95(1.4)	0.20

Table III: Patients condition at the end of the investigation.

Condition	**GI**	**GII**
Excellent(no,%)	6(10.3)	15(26.3)
Moderate(no,%)	34(58.6)	37(64.9)
Poor(no,%)	18(31.03)	5(8.8)

DISCUSSION

Asthma has remarkable limitation of activity. It is characterized by long standing airway inflammation, airway edema, bronchoconstriction and airway hyper responsiveness causing wheezing, shortness of breath, chest tightness and cough. The severity of the disease is variable with time and attacks of exacerbation commonly need intervention. The initial step of management in acute attacks of asthma is fast reversal of bronchospasm and decrease of airway inflammation. For this, oral steroids are intensively efficient for minimizing clinical features in children. Although the 2019 British protocol on the Management of Asthma indicate inhaled β2 agonists as fist strategy of management for acute asthma attacks in children, early administration of oral steroid is indicated with prednisone being the agent of selection. 5–25% of patient's relapse, needing admission for therapy of consecutive attacks. Relapse following prednisone is caused by the unpleasant bitter taste of the agent, adverse-effects like vomiting and multiple dose protocol of 3–5 days that decreases patient compliance.

In this investigation of management for patients with severe acute bronchial asthma, the enhancement in lung function during the primary 6 hours in patients managed with oral prednisone was double that in patients managed with inhaled fluticasone. The percentage of admission in the inhaled fluticasone group was thrice that in the oral prednisone group. There was a remarkable advantage of corticosteroids 2-4 hours following receiving in patients with acute severe bronchial asthma.[16] Pathogenesis theories are up-regulation of β2-adrenergic receptors, mucosal vasoconstriction and a reduction in airway edema.

Oral prednisone and nebulized dexamethasone experienced comparable potency in the management of bronchial asthma.[6] Dexamethasone is active systemically as it is not metabolized on the first pass via the liver.[6] The absorption of dexamethasone was ameliorated by nebulization, causing increased percentage of oropharyngeal deposition of the drug.[14] Less than 1% of fluticasone is absorbed from the gastrointestinal tract.[10], with less systemic actions. Inhaled flunisolide had better pulmonary function than placebo.[7] The dose of flunisolide was high and during three-hours.

In this investigation, bad outcome in the inhaled fluticasone group is caused by inferior delivery of the agent to the lung due to intense airway narrowing. To reduce this event, an increased dose of fluticasone was selected by pre-therapy with nebulized bronchodilators using a deep-inhalation method. Airways blocked by mucus might receive less inhaled fluticasone, while systemic corticosteroids could be delivered anywhere with a blood supply. There was no enhancement following three hours in the fluticasone group explains the maximal action of the β2-adrenergic agonist. Age had no remarkable action on the discrepancy in potency between both groups. This investigation included patients with acute severe bronchial asthma with more

acute inflammation and mucous plugging which is difficult to be managed with inhaled corticosteroids.

In this investigation, the maintenance of management following discharge caused comparable enhancement of lung function in both groups. Following primary management using prednisolone, treatment with budesonide or prednisolone for one week caused comparable percentages of recovery.[9] Patients with mild attacks of asthma could be managed with increased doses of fluticasone.[8] There was a remarkable clinical advantage of increased doses of inhaled corticosteroids in patients with the start of an upper respiratory tract infection and with the first clinical features of asthma, respectively.[17] There were large discrepancies in the percentages of admission between the groups. Our results should not be generalized to children with mild attacks of asthma.

IN CONCLUSION

Patients with severe acute bronchial asthma must be managed with oral prednisone and not with inhaled fluticasone.

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