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Original Article

Systemic Corticosteroids with or without Nebulized Budesonide for Treatment of Acute Severe Asthma Exacerbations in the Emergency Room: A retrospective Study

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Abstract

Background: Acute severe asthma exacerbations remains a treatment challenge. The value of inhaled added to systemic corticosteroids in the treatment of acute severe asthma is not well addressed.

The Aim of the Work: This study aimed to investigate the value of inhaled corticosteroids added to systemic corticosteroids compared to systemic corticosteroids alone in the management of acute severe asthma exacerbation treated in emergency room..

Patients and Methods: 115 patients were included and divided into study [n = 55] included patients received inhaled hydrocortisone 100 mg IV, nebulized ipratropium bromide 500µg , Salbutamol 0.5 % respiratory solution and budesonide 0.5 mg at 20-, 40-, 60- and 120-min; and the comparison [n= 60] group received the standard protocol only. The following data were documented: Respiratory rate, heart rate, blood pressure, peak expiratory flow rate, were documented over 3 hours after initiation of treatment. The Primary outcome was improvement of PEF and the admission rate.

Results: The basal PEF [L/min] ranged between 120 and 210, with no significant differences. There was progressive reduction of PEF overtime in both groups. However, the percentage of reduction was significantly higher in the study than the comparison groups [99.86±16.64 vs 89.52±22.25, respectively]. The difference between groups was significant at 120 to 180 minutes. Respiratory rate was significantly and progressively reduced in both the study and the comparison groups at the end of assessment than the basal values. The percentage of reduction was significantly higher among the study than the comparison groups [38.22±4.20 vs 36.21±4.14, respectively, p = 0.011]. The study and comparison groups showed non-significant differences, as hospitalization was recorded for 29.1% and 35.0% of the study and the comparison groups respectively.

Conclusion: The association of nebulized budesonide with systemic corticosteroids provides mild additional effects than systemic corticosteroids alone for severe asthma in emergency department.

Keywords: Bronchial Asthma; Corticosteroids; Inhalers; The Peak Expiratory Flow.

INTRODUCTION

Bronchial asthma is a major cause of significant morbidity and mortality all over the world and middle east countries are not an exception. It is a chronic heterogenous obstructive airway disease, and interaction between multiple factors [e.g., genetic, environmental and lifestyle] play a role in asthma pathogenesis. In addition, asthma is strongly linked to allergy or atopy and characteristically respond to cortico-steroids [1-3].

Systemic corticosteroids [SC] are the gold-standard approach for treatment of acute exacerbation of bronchial asthma [BA]. However, it requires 6-24 hours to reach the optimal effects on the pulmonary function [4,5]. Thus, inhaled short acting bronchodilators and adequate oxygenation are required for emergency management of BA. The use of inhaled corticosteroids in acute BA returns to attract attention in the past years [6-10].

Previous studies in children and adults have shown a reasonable effect [90 to 120 minutes] on pulmonary functions in the treatment of acute asthma [11-15].

Edmonds *et al.* [12] published a systematic review on the effectiveness of inhaled corticosteroids in the treatment of acute asthma in emergency department [ED] and concluded that inhaled corticosteroids are beneficial when compared to placebo. However, studies in children reported contradictory results [16,17].

The available evidence regarding efficacy of inhaled corticosteroids alone in treatment of acute BA in the ED is insufficient, especially when compared to systemic corticosteroids. In addition, the value of adding inhaled to systemic corticosteroids for the significant change of pulmonary function or clinical outcomes is still under investigation [12,18].

The systemic corticosteroids aimed to evaluate the role of systemic with or without high repeated doses of inhaled corticosteroids for treatment of acute asthma exacerbation in the emergency department.

We hypothesized that the introduction of inhaled high repeated doses of corticosteroids to systemic corticosteroids will be more effective in improving the pulmonary function.

PATIENTS AND METHODS

Study design: A retrospective comparative study.

Study setting and time: The study was completed in the emergency department of the Al-Azhar Damietta Faculty of Medicine University Hospitals, between January 2021 and March 2024.

Inclusion criteria: we included adult [age between 18 and 50 years] patients with confirmed diagnosis of BA according to 2021 Global Initiative of Asthma [GINA] guidelines [19], PEF [peak expiratory flow rate < 50% of predicted, with one or more of accessory muscle activity, HR [heart rate] > 100 beats/minute], RR [respiratory rate] > 25 cycles/minute, limitation of speaking ability. In addition, the informed consent of the patient to participate [informed written consent signature was obtained]

Exclusion criteria: Temperature > 38ºC, history of systemic diseases [e.g., cardiac, renal, hepatic] and for females, pregnancy was an exclusion criterion.

Ethical considerations: The study protocol was reviewed and accepted by the local research and ethics committee board of the Damietta Faculty of Medicine, Al-Azhar University [Damietta] [IRB number: DFM-IRB00012367-23-07-025].

Patients were divided into two groups according to the use of nebulized budesonide. The first [assigned as the study group; n = 55] included patients received hydrocortisone 100 mg IV, Nebulized Ipratropium bromide 500µg, Salbutamol 0.5% respiratory solution and budesonide 0.5 mg at 20-, 40-, 60- and 120-min. the oxygen flow rate was 7 L/min. Patients in the comparison [control; n= 60] group received the same treatment as in the first group, except budesonide.

Patient demographics, asthma severity, previous treatment, duration of symptoms, previous hospitalization and/or mechanical ventilation for asthma, were collected. Before initiation of treatment and then 30, 60, 90, 120, 150 and 180 minutes after treatment, the following data were documented: Respiratory rate, heart rate, blood pressure, peak expiratory flow rate, and activation of accessory muscles of respiration.

The peak expiratory flow [PEF] was measured by a peak-flow meter for three successive measures [Micro-PeaK® Cardinal Health, UK]; and the highest of these measures was included in the statistical analysis.

The presence of dyspnea was subjectively measured by the patient him/herself. The difficulty of breathing was assigned a score of 0 [absent dyspnea], 1 [minimal dyspnea], 2 [moderate dyspnea] and 3 for severe dyspnea. The need for admission and mechanical ventilation was recorded and the treatment protocol was stopped when aggravation of symptoms needs mechanical ventilation. At the end of the 180 minutes of post-treatment follow up, any side effects were documented [e.g., palpitation, tremor, anxiety, headache, and dry mouth]. The decision after treatment protocol included patient discharge from the ED or admission to the inpatient or intensive care unit to complete the treatment. The patient discharge was built on the following criteria: no involvement of accessory muscle of respiration, absent or minimal sibilant rhonchi, absent dyspnea, PEF more than 60% of predicted. The treatment protocol after discharge

included prednisone 40mg/day for 7 days, short-acting beta-agonists and a follow-up outpatient visit every week for 4 weeks. **The Primary outcome** measures of the current study included significant improvement of PEF and the rate of admission to inpatient or intensive care unit. Other outcomes measures were considered as secondary outcome [e.g., clinical data, RR, HR, and side effects]

Statistical analysis: Data was fed to personal computer after appropriate coding and anonymization. Continuous numerical variables were expressed as mean [the measure of central tendency] and standard deviation [SD] [the measure of dispersion]. Categorical variables were summarized by the relative frequencies and percentages of each group. Continuous variables were compared by Student's "*t*" test or the Mann-Whitney "U: test according to normality of distribution. Chi Square or Fisher's exact tests were used to test association between categorical variables. A *p* value of less than 0.05 was taken as significant for all statistical tests.

RESULTS

The current work included 115 subjects with acute severe asthma exacerbations, 55 of them received systemic corticosteroids plus nebulized budesonide [the study group], while the 60 subjects received systemic corticosteroids only [The comparison group]. The patient age ranged between 21 to 65 years, with no significant difference between the study and comparison groups [39.67 ± 9.83 vs 40.15 ± 10.22 years, respectively]. There was a slight increase of males in both groups, with no significant differences. In addition, both groups were comparable regarding to long-term drug therapy and previous hospitalization for asthma in the previous year before the current attack [Table 1]. On arrival to emergency room, the heart rate ranged between 82 and 125 beats/minute, while systolic blood pressure ranged between 90 and 170 mmHg and diastolic blood pressure ranged between 60 and 125 mmHg. The duration of the last attack [hours] ranged between 24 and 72 hours; the respiratory rate ranged between 25 to 35 cycles/minute and oxygen saturation ranged between 92 and 96%. The PEF [L/min] ranged between 120 and 210, while its percent of predicted ranged between 24 and 41%, with no significant differences between groups. Furthermore, the PEF% lower than or equal to 30.0% were 41.8% and 40.0% of the study and comparison groups respectively, with no significant differences [Table 2].

The PEF was comparable at the basal values and up to the 90 minutes of starting therapy. In both groups, there was progressive reduction of PEF overtime in both groups. However, the percentage of reduction was significantly higher in the study than the comparison groups [99.86±16.64 vs 89.52±22.25, respectively]. The difference between groups was significant at 120 to 180 minutes [Table 3]. Respiratory rate was significantly and progressively reduced in both the study and the comparison groups at the end of assessment than the basal values. The percentage of reduction was significantly higher among the study than the comparison groups [38.22±4.20 vs 36.21±4.14, respectively, p = 0.011]. The difference between both groups was comparable overtime except significant decrease of RR at 60 and 90 minutes. On the contrary, HR progressively reduced in the study and progressively increased in the comparison groups over time. The difference becomes significant from 120 minutes till the end of collected data [180 minutes] [Table 4].

Regarding outcome [hospitalization] and side effects, the study and comparison groups showed non-significant differences, as hospitalization was recorded for 29.1% and 35.0% of the study and the comparison groups respectively [Table 5].

Table [1]: Comparison between study groups regarding patient demographics and past history

Variables		The study group	The comparison group	Test	P
Age [years]	Mean±SD	39.67±9.83	40.15±10.22	0.255	0.799
	Min. – Max.	24-62	21-65		
Sex [n,%]	Female	24 [43.6%]	19[31.7%]	1.756	0.185
	Male	31 [56.4%]	41 [68.3%]		
Long-term Drug therapy	Long term β-agonists	31 [56.4%]	30 [50.0%]	0.47	0.50
	Inhaled corticosteroids	27[49.1%]	30 [50.0%]	0.99	0.32
	Systemic corticosteroids	4 [7.3%]	7 [11.7%]	0.64	0.42
	Theophylline	6 [10.9%]	9 [15.0%]	0.42	0.52
Hospitalization for acute Asthma in the Previous year	None	44 [80.0%]	47 [78.3%]	1.77	0.62
	Once	7 [12.7%]	11 [18.3%]		
	Twice	3 [5.5%]	1[1.7%]		
	Thrice or more	1 [1.8%]	1[1.7%]		

Table [2]: Comparison between study groups regarding patient and asthma characteristics on arrival to emergency room

Variables			The study group	The comparison group	Test	P
Heart rate [b/min]		Mean ±SD	97.89±10.52	96.80±8.89	0.60	0.55
		Min. – Max.	85-125	82-122		
Blood pressure [mmHg]	Systolic	Mean ±SD	129.81±18.60	126.58±16.55	0.99	0.33
		Min. – Max.	90-170	90-170		
	Diastolic	Mean ±SD	82.72±16.18	80.91±13.10	0.66	0.51
		Min. – Max.	60-125	60-110		
Duration of the last attack [h]		Mean ±SD	35.35±9.91	36.20±11.16	0.43	0.67
		Min. – Max.	24-72	24-72		
Respiratory rate [cycle/minute]		Mean ±SD	30.02±1.89	29.65±1.34	1.21	0.23
		Min. – Max.	25-35	27-32		
Oxygen saturation Percentage		Mean ±SD	94.47±0.69	94.42±0.79	0.40	0.69
		Min. – Max.	93-96	92-96		
PEF [L/min]		Mean ±SD	157.23±15.48	158.53±14.33	0.47	0.64
		Min. – Max.	136-210	120-190		
PEF percent of Predicted		Mean ±SD	31.44±2.83	31.94±3.18	0.89	0.38
		Min. – Max.	27 - 40	24 – 41		
PEF% of Predicted ≤ 30			23 [41.8%]	24 [40.0%]	0.04	0.84

Table [3]: Changes of PEF over time

PEF [L/min]	The study group	The comparison group	Test	P
Basal values	157.23±15.48	158.53±14.33	0.47	0.64
PEF 30	211.27±18.00	207.73±14.33	1.17	0.24
PEF 60	264.80±18.24	260.32±15.31	1.43	0.16
PEF 90	285.35±18.98	280.73±16.30	1.40	0.17
PEF120	302.16±19.96	292.95±24.56	***2.19***	***0.030****
PEF 150	313.32±19.93	305.47±17.44	***2.25***	***0.026****
PEF180	312.70±25.12	298.35±28.42	***2.85***	***0.005****
% of difference	99.86±16.64	89.52±22.25	***2.80***	***0.006****

Table [4]: Changes of RR and HR over time

		The study group	The comparison group	Test	P
RR [Cycle/min]	Basal values	30.02±1.89	29.65±1.34	1.21	0.23
	RR 30	27.00±1.53	27.48±1.64	1.63	0.11
	RR 60	**24.60±1.73**	**26.10±1.42**	**5.10**	**<0.001***
	RR 90	**21.20±1.52**	**23.13±1.66**	**6.49**	**<0.001***
	RR 120	20.10±1.38	20.42±1.46	1.23	0.22
	RR 150	19.52±1.73	19.96±1.35	1.82	0.13
	RR180	18.55±1.74	18.90±1.31	1.24	0.21
	% of reduction	**38.22±4.20**	**36.21±4.14**	**2.58**	**0.011***
HR [beat/min]	Basal values	97.89±10.52	96.80±8.89	0.60	0.55
	HR 30	97.90±10.35	97.56±8.36	0.19	0.86
	HR 60	97.89±9.46	98.23±7.79	0.21	0.83
	HR 90	97.41 ±8.73	98.53±7.58	0.73	0.46
	HR 120	**96.20±8.12**	**99.72±7.57**	**2.40**	**0.018***
	HR 150	**95.14±6.79**	**98.14±6.68**	**2.71**	**0.008***
	HR 180	**94.75±6.63**	**98.95±7.00**	**3.29**	**0.001***
	% of change	**-2.76±5.62**	**2.64±7.36**	**4.39**	**<0.001***

Table [5]: Outcome among study groups

		The study group	The comparison group	Test	P
Hospitalization		16[29.1%]	21 [35.0%]	0.45	0.49
Side effects	Palpitation	9[16.4%]	11 [18.3%]	0.08	0.78
	Tremors	7 [12.7%]	10 [16.7%]	0.35	0.55
	Headache	5 [9.1%]	8 [13.3%]	0.51	0.47
	Dry mouth	3 [5.5%]	7[11.7%]	1.39	0.24

DISCUSSION

The current work retrospectively evaluated the value of nebulized budesonide when added to systemic corticosteroids for emergency treatment of acute exacerbation of severe asthma. It is associated with significant improvement in the PEF starting 2 hours after initiation of therapy till the end of the assessment time [180 minutes]. In addition, the reduction of respiratory rate [compared to basal values] was significantly marked in the study than the comparison group and heart rate was significantly reduced with nebulized budesonide overtime but increased overtime in the comparison group. The rate of admission [hospitalization] and side effects were reduced with nebulized budesonide. However, the difference did not reach statistical significance. **Marghli *et al.*** [18] in a prospective randomized controlled trial, reported that the addition of nebulized budesonide showed no significant effects on the admission rate, the discharge criteria before 3 hours [end of treatment protocol], PEF improvement, decreased dyspnea, side effects and the reduction of respiratory rate. However, the heart rate was higher in the study than the control group. These results are partially agree with the current work, especially regarding outcome [admission rate and side effects] and heart rate. But different regarding other variables. The different nature of study design [prospective versus retrospective] and number of included subjects [50 versus 115] in their study and current study may explain the different results. In addition, they excluded cases over the age of 50 years, but we did not.

In the emergency situations, the use of systemic corticosteroids with repeated nebulization of different drugs [beta-2 agonists, anticholinergic] and adequate oxygenation is the mainstay of treatment of acute asthma attacks, as reported previously. Inhaled drugs [mainly corticosteroids] provide acute response due to its topical anti-inflammatory action. But, the anti-inflammatory response of system corticosteroids usually delayed for hours or days. This is the basis of the use of inhaled drugs besides systemic corticosteroids for treatment of acute severe asthma attacks treated in the emergency room [20]. In addition, inhaled corticosteroids reduced airway blood flow through modulation of sympathetic nervous system control, leading to vasoconstriction of the airway vasculature. However, this is a transient effect, peaked in 30 minutes, then returns to basal values within 60 to 90 minutes [21].

The reduced flow of airway blood vessels may explain the partial beneficial bronchodilator actions of inhaled corticosteroids as their clearance from airway is reduced. This may reflect the value of concomitant administration of inhaled corticosteroids with other systemic bronchodilators [22].

Previous literatures both in adults and children showed favorable outcome with the use of inhaled corticosteroids in addition to systemic bronchodilators for treatment of acute exacerbations, with improvement of hemodynamic physiological data [11,23,24]. A meta-analysis performed by **Edmonds *et al.*** [12] showed a significant reduction in the admission rate in patients treated by inhaled corticosteroids than placebo [only 1 patient out of 8 patients received inhaled corticosteroids, needs admission]. However, other study reported heterogeneous even contradictory results on the value of inhaled cortico-steroids in treatment of acute asthma exacerbations[16,25]. **Guttman *et al.*** [26] included 60 patients with acute asthma treated in the emergency room. Patients received a salbutamol nebulization [base, 30 min, 1h, 2h, 4h, 6h, 8h and 10h] plus 80mg of intravenous methylprednisolone at the time inclusion and 40mg after 6 hours. Patients assigned as the study group additionally received 7mg over 8 hours [base, 30 min, 1 h, 2h, 4h, 6h and 8h] of beclomethasone-dipropionate through a metered dose inhaler, while placebo used in the control group in the same pattern. The authors recorded a significant increase in FEV1, predicted FEV and PEF percentage change [$p < 0.001$]. This was associated with significant reduction of dyspnea score an respiratory rate. A plateau was recorded at 120 minutes and only minor [non-significant] changes were recorded thereafter. In another study **Bateman *et al.*** [27] compared budesonide / formoterol to formoterol alone in 115 adult asthma. They showed a comparable rapid relief of bronchoconstriction in the two groups with no significant differences regarding treatment success or failure.

Finally, in the recent update of The Global Initiative for Asthma [GINA] guidelines advised the use of inhaled corticosteroids must be added to medications of asthma. They prohibited the treatment of asthma with short acting beta agonists alone [28]. This was initiated in GINA guidelines 2022, where it recommends that all adults, adolescents and most children with asthma must receive ICS-containing therapy to reduce the risk of exacerbations, on regular basis or [for adults and adolescents with "mild" asthma] as combination ICS-formoterol taken as needed for symptom relief [29].

Limitations: Our study has some limitations. First, the retrospective nature with potential bias and objectivity of admission and small number of included subjects. Thus, future studies are recommended to validate results and test other inhalers.

Conclusion: The association of nebulized budesonide with systemic corticosteroids provides mild additional effects than systemic corticosteroids alone for severe asthma in emergency department.

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