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Original article

An assessment of asthma exacerbations in pediatric patients using a long-acting B2-agonist plus inhaled corticosteroid versus an inhaled corticosteroid alone

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ABSTRACT

Background: An asthma exacerbation is an anticipated sudden worsening of the disease severity, which usually does not respond to conservative therapy. The management of asthma depends on the severity of the disease symptoms, which includes an inhaled corticosteroid (ICS) and a bronchodilator. This study aimed to assess the efficacy of combining a long-acting B2-agonist (LABA) with ICS, compared to ICS alone, to reduce the incidence of asthma exacerbations in pediatric patients, diagnosed with severe persistent asthma.

Methods: A retrospective analysis of the medical records was conducted for 586 children, admitted to the Emergency Department (ED) at King Abdullah Specialized Children Hospital in Riyadh, Saudi Arabia, for the management of severe persistent asthma symptoms, from January 2016 to September 2019.

Results: The majority (n = 480, 81.9%) of the patients received fluticasone (Flovent)® as the standard of care ICS treatment for controlling asthma, and a small proportion (n = 106, 18.1%) were treated with a combination of LABA and ICS. A significant increase in the frequency of recurrent asthma exacerbation episodes occurred in the group receiving ICS alone (98.5%), compared to 67.0% in the combination group ($p < 0.0001$). Moderate to severe exacerbations were significantly higher in the ICS group compared to the combination group (95.6% versus 84.5%, respectively, $p = 0.0005$).

Conclusions: The current results confirm the substantial efficacy of the LABA/ICS combination therapy in reducing the incidence and severity of asthma exacerbations in pediatric patients, compared to ICS alone.

1. Introduction

Asthma is a prevalent chronic disease, affecting the quality of life of patients and their families, due to frequent emergency visits and hospitalizations. According to the United States (US) Centers for Disease Control and Prevention (CDC), approximately 60% of children with current asthma have persistent symptoms. During 2006–2010, the prevalence of intermittent and persistent asthma in pediatric patients varied between countries, ranging from 45.0% to 74.4% (National Center for Environmental Health. Asthma Severity among Children with Current Asthma, 2015). In Saudi Arabia, the prevalence of asthma in pediatric patients has also exponentially increased in the past three decades, ranging from 8% to 25% (Al-Moamary et al., 2016). Several factors contributed to such an increase, including tobacco smoke, dietary variations, social development, and environmental changes. Although the overall prevalence of asthma in Saudi Arabia is lower than in most western countries, asthma symptoms in many patients are poorly controlled (Moradi-Lakeh et al., 2015).

An asthma exacerbation is an anticipated acute complication of asthma, which does not adequately respond to the short-acting beta2-agonist (SABA) bronchodilators. Asthma exacerbations are usually developed due to an exaggerated response of the pul-

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monary airways to a provoking causative agent. For example, a respiratory viral infection is the most frequent exposure factor to trigger a sudden severe asthma exacerbation, that may last for several days (Wark et al., 2006). The recurrence of these serious acute episodes of breathing difficultly requires urgent treatment that usually involves the use of systemic corticosteroids (Fuhlbrigge et al., 2012). Even though the current therapeutic regimens effectively alleviate asthma symptoms, some patients continue to experience asthma exacerbations.

Several initiatives have been considered to prevent asthma exacerbations, such as doubling the dose of the inhaled corticosteroid (ICS) (Harrison et al., 2004), or the combined use of a long-acting beta2 agonist (LABA) and ICS (Xia et al., 2013). A number of randomized controlled trials reported a significant reduction in asthma exacerbations in patients using the combination therapy, compared to LABA or ICS alone (Bateman et al., 2014; Razi et al., 2015; Lee et al., 2016). The combination therapy diminished the risk of asthma-related serious events such as hospitalization and death (Peters et al., 2016). However, other studies failed to demonstrate any significant difference between these therapies (Beasly et. al, 2015; Stemple et al., 2016a, 2016b). Due to the conflicting findings, there is no current strong evidence to support using either regimen to prevent asthma exacerbations. In addition, almost all literature reflects an adult or adolescent population, rather than a pediatric population. In the current study, we aimed to assess the efficacy of combining LABA with ICS versus ICS alone in reducing the incidence of asthma exacerbations in pediatric patients diagnosed with severe persistent asthma. We hypothesized that the combination regimen would be more effective than the monotherapy in preventing asthma exacerbations in children.

2. Methods

2.1. Design and settings

A retrospective review of the patients' medical records was conducted at King Abdullah Specialized Children Hospital (KASCH) in Riyadh, Saudi Arabia, an academic tertiary-care, and Joint Commission International (JCI) accredited institution. Initially, 3498 records of patients admitted to the KASCH Emergency Department (ED) with acute respiratory symptoms from January 2016 to September 2019 were screened. Only 586 children, younger than 18 years, with an established diagnosis of severe persistent asthma, were included.

Patients who did not have a prior diagnosis of asthma, patients with chronic obstructive pulmonary disease (COPD), or with an incomplete medical record of asthma-related information were excluded. The data were collected using a structured data collection format, including demographic information, in addition to the medical and asthma treatment history for the past 6 months.

2.2. Outcome measures

The primary outcome of the study was the frequency of asthma exacerbations in the last 4 weeks prior to admission to ED, in children treated with ICS monotherapy or with LABA and ICS as combination therapy for severe persistent asthma. Severe persistent asthma and asthma exacerbation cases were defined according to the International Classification of Diseases, Tenth Revision (ICD-10-CM), Clinical Modification, codes J45.50 and J46 that was based on the NIH guidelines (Appendix I): mild, moderate, and severe exacerbation. The diagnosis was confirmed by reviewing the patient's medical chart.

The secondary outcomes were the association of the demographic characteristics (age, gender, weight, BMI percentile) and clinical factors (allergy, type of ICS, and comorbidities) with the incidence of asthma exacerbation. The study was approved by the Institutional Review Board of the King Abdullah International Medical Research Center (KAIMRC).

2.3. Statistical analysis

Results are expressed as mean ± standard deviation (SD) or as median with the interquartile range for continuous data, and as proportions for the categorical variables. The descriptive and statistical analyses of the variables were performed by Student's *t*-test or chi-square/Fisher exact tests. The odds ratios were calculated to determine the association between the patient factors and the frequency of asthma exacerbations. Statistical significance was considered at a p-value<0.05. We used SPSS statistics software Version 21(IBM, Armonk, NY) for the analyses.

3. Results

The sample size realized as 586 asthmatic children admitted to the pediatric ED for the management of severe asthma symptoms. The mean age was 7.74 ± 3.6 years, with a median value of 7 years (range 0.25–17). Two-thirds of the sample (n = 387, 66.0%) were male. The majority of the sample were underweight (75.9%), and 84.5% presented with upper respiratory infections (URIs) at the time of enrollment (Table 1).

All the participants received fluticasone oral inhalation (Flovent)® as the standard of care ICS treatment for controlling asthma. Table 2 indicates the distribution of the sample by inhaled treatment. The majority (81.9%) were using ICS alone, 18.1% were treated with the LABA/ICS combination therapy. Significant differences were found between the two treatment groups, for most of the variables. Although the blood oxygen saturation (SpO_2) levels were comparable between the two groups, the frequency and severity of exacerbations varied significantly.

The vast majority (98.5%) in the ICS group had at least one asthma exacerbation episode during the four weeks prior to the hospitalization, compared to 67.0% in the combination group. The

Table 1
General profile of the sample (n = 586).

Variable	n (%)
Age (in years)	
Mean ± SD	7.74 ± (3.6)
Median (range)	7 (0.25–17)
Gender n (%)	
Male	387 (66.0)
Female	199 (34.0)
BMI category n (%)	
Underweight	445 (75.9)
Healthy weight	90 (15.4)
Overweight	26 (4.4)
Obese	25 (4.3)
Allergies n (%)	77 (13.1)
Drugs	54 (70.1)
Foods	20 (26.0)
Others	3 (3.9)
Comorbidities n (%)	
Diabetes	2 (0.3)
Epilepsy	10 (1.7)
URIs	495 (84.5)
Heart problem	24 (4.1)
Respiratory problems*	18 (3.1)
Skin problems	10 (1.7)
Immunodeficiency	4 (0.7)
Gastrointestinal problems	2 (0.3)
Others	36 (6.1)

* Not including asthma.

Table 2
Distribution of sample by inhaled treatment.

Variable	ICS alone n = 480 (81.9%)	ICS + LABA n = 106 (18.1%)	p-value
Age in years			<0.0001
Mean ± SD	6.96 ± 3.1	11.28 ± 3.8	
Median (range)	6 (1–16)	12 (0.25–17)	
Gender n (%)			0.0066
Male	305 (63.5%)	82 (77.4%)	
Female	175 (36.5%)	24 (22.6%)	
BMI n (%)			<0.0001
Underweight	395 (82.3%)	50 (47.2%)	
Normal weight	61 (12.7%)	29 (27.4%)	
Overweight/obesity	24 (5.0%)	27 (25.5%)	
Heart rate per min			<0.0001
Mean ± SD	129.9 ± 21.3	117.9 ± 20.5	
Median (range)	128 (76–211)	116 (79–170)	
Respiratory rate per min			0.0017
Mean ± SD	32.4 ± 7.8	28.6 ± 10.0	
Median (range)	30 (20–76)	26 (20–87)	
Oxygen saturation SpO_2 %			0.3476
Mean ± SD	96.4 ± 3.9	96.2 ± 6.4	
Median (range)	97 (73–100)	97 (47–100)	
Allergies (not respiratory) n (%)	54 (11.2%)	23 (21.7%)	0.0040
URIs n (%)	423 (88,1%)	72 (67.9%)	<0.0001
Diabetes n (%)	2 (0.4%)	0 (0.0%)	0.5056
Epilepsy n (%)	9 (1.9%)	1 (0.9%)	0.5027
Number of Exacerbations*	473 (98.5%)	71 (67.0%)	<0.0001
Number of Exacerbations*			<0.0001
Mean ± SD	5.33 ± 5.0	3.22 ± 4.8	
Median (range)	4 (0–38)	2 (0–23)	
Severity of Exacerbation	(n = 473)	(n = 71)	0.0005
Mild	21 (4.4%)	11 (15.5%)	
Moderate	384 (81.2%)	55 (77.5%)	
Severe	68 (14.4%)	5 (7.0%)	

* During the past 4 weeks before hospitalization.

ICS group had a higher risk of asthma exacerbations than the combination group ($p < 0.0001$). A higher number in the ICS group had moderate to severe exacerbations, compared to the combination group (95.6% versus 84.5%, respectively, $p = 0.0005$).

Factors associated with the increased frequency of asthma exacerbations in the sample are displayed in Table 3. Patients who were younger (<7.74 years, the mean age of the sample), male gender, underweight, and with a history of URIs were at a higher risk of asthma exacerbations. Obese and underweight children had more frequent asthma exacerbations compared to normal-weight patients ($p = 0.0046$ and $p = 0.0229$ respectively). There was no difference in the incidence or severity of asthma exacerbations between patients using either Symbicort® Turbohaler or Seretide® Evohaler combination product.

4. Discussion

Despite the availability of various treatments, asthma exacerbation is still a significant complication and a major cause of hospitalization or death in asthma patients. The introduction of LABA was considered a major breakthrough in the treatment of patients; however, several safety concerns were raised due to the use of LABA in pediatric patients (Xia et al., 2013). Nelson et al., 2006 reported a small but statistically significant increase in the respiratory- and asthma-related deaths in patients, older than 12 years, who received salmeterol compared with placebo, with a greater risk in non-Caucasian people (Nelson et al., 2006).

Previously, studies reported no significant difference in the number of asthma exacerbations in children receiving LABA treatment with either salmeterol (Von Berg et al., 1998) or formoterol (Bensch et al., 2002) versus the placebo group. In 2003, a *meta*-analysis, including 8 randomized control trials, concluded that there was no additional protection from asthma exacerbations in pediatric patients with mild-to-severe persistent asthma receiving LABA, compared to SABA, ICS, or placebo (Bisgaard et al., 2003). Consequently, in February 2010, the FDA issued a safety announcement warning against the long-term monotherapy use of LABA in adult and pediatric patients, without a rescue SABA or ICS. It was assumed that LABA monotherapy might increase the risk of serious asthma exacerbations. However, after evaluating several FDA mandated-post-market safety clinical trials conducted by the LABA manufacturers, assessing LABA safety, an updated circulation was issued by FDA in December 2017. The new safety communication testified that "*there is no significant increase in the risk of serious asthma outcomes with LABA used in combination with ICS*" (U.S. Food and Drug Administration. FDA Drug Safety Communication 2017).

Several recent studies reported positive outcomes for LABA use in asthma patients when added to the existing ICS treatment. LABA therapy was well tolerated by most patients and it was associated with a significant reduction in serious asthma-related events and the overall risk of hospitalization due to asthma exacerbation was also lowered in patients receiving the LABA/ICS combination therapy, compared to the groups taking a SABA or ICS only (U.S. Food and Drug Administration. FDA Drug Safety Communication 2017; Lee et al., 2016; Guo et al., 2011; Weinstein et al., 2019). Despite being limited, similar results were reported in studies conducted with pediatric patients with severe asthma to confirm the efficacy and safety of the concurrent use of LABA and ICS (Razi et al., 2015; Bensch et al., 2002; Stemple et al., 2016a, 2016b). A significant sustained improvement in lung function was reported in the pediatric patients receiving the LABA/ICS combination therapy; however, no statistical difference was found between the low and high doses of LABA (Zimmerman et al., 2004).

These findings are consistent with the results of the current study demonstrating a significant reduction in the frequency and severity of recurrent asthma exacerbation episodes in pediatric patients receiving the LABA/ICS combination therapy, compared to ICS alone. The current study did not find a significant difference in the incidence or severity of asthma exacerbations between patients using a Symbicort® Turbohaler (formoterol–budesonide) or the Seretide® Evohaler (salmeterol–fluticasone propionate) combination product.

In addition to the ICS monotherapy, the current study identified a number of factors associated with an increase in the incidence of asthma exacerbations in children. Unlike adult patients, where an older age was associated with a higher risk (Price et al., 2016; Blakey et al., 2017), children younger than 8 years old were at a higher risk for asthma exacerbations. Similar findings were reported in literature (Engelkes et al., 2016; Turner et al., 2018; Bloom et al., 2018). A recent article suggested that poor adherence of pediatric patients to the appropriate inhaler technique could be the main obstacle for asthma control, which negatively affects asthma exacerbations (Kaplan et al., 2019). Other factors increasing the risk of asthma exacerbations include male gender, low BMI, and patients with a history of URIs. In contrast to the current findings, Quinto et al. 2011 reported an increased risk of asthma exacerbations in overweight and obese children that necessitated high doses of beta-agonists and oral corticosteroids, compared with normal-weight children (Quinto et al., 2011). Several other factors have also been reported by some studies with pediatric patients, including asthma severity (Bloom et al., 2018), prior history of exacerbations, lower respiratory tract infections (Turner et al., 2018), reduced lung function (Blakey et al., 2017), high eosinophil count, (Blakey et al., 2017), and the spring and fall seasons (Engelkes et al., 2016).

Table 3
Association between patients' factors and incidence of asthma exacerbation.

Variable/Risk Factor	Asthma Exacerbation				OR (95% CI)	p-value
	Positive n = 544		Negative n = 42			
	n	%	n	%		
Age in years						
<Mean (7.74)	316	58.1	10	23.8	4.44	0.0001
≥Mean	228	41.9	32	76.2	(2.14–9.21)	
Gender n (%)						
Male	351	64.5	36	85.7	3.30	0.0080
Female	193	35.5	6	14.3	(1.37–7.97)	
BMI n (%)						
Under/Normal weight	508	93.4	27	64.3	7.84	<0.0001
Overweight/obesity	36	6.6	15	35.7	(3.83–16.04)	
Allergies n (%)	72	13.2	5	11.9	1.13	0.8059
					(0.43–2.97)	
URIs n (%)	472	86.8	23	54.8	5.42	<0.0001
					(2.81–10.44)	
Diabetes n (%)	2	0.4	0	0.0	0.39	0.5473
					(0.02–8.29)	
Epilepsy n (%)	10	1.8	0	0.0	1.67	0.7248
					(0.10–28.99)	
Inhaled treatment n (%)						
Fluticasone only	473	86.9	7	16.7	0.03	<0.0001
					(0.01–0.07)	
Combination inhalers	71	13.1	35	83.3		
Combination inhalers n (%)	(n = 71)		(n = 35)			
Symbicort® Turbohaler	6	8.5	3	8.6	1.02	0.9833
Seretide® Evohaler	65	91.5	32	91.4	(0.24–4.33)	

According to the Global Initiative for Asthma (GINA) report 2020, controlling persistent asthma symptoms or exacerbations affecting all age groups continues to be a major health challenge for all countries globally (Global Initiative for Asthma 2020). The GINA report provides a stepwise approach for the management of asthma. However, current treatment guidelines for pediatric asthma were still based on limited evidence and are primarily based on recommendations extrapolated from adult studies (Kaplan et al., 2019). The initial treatment of severe asthma in pediatrics is SABA, as required, as a reliever of asthma attacks, and high doses of ICS as the controller drug. LABA and other add-on therapies, such as leukotriene receptor antagonists and methylxanthines can later be combined with ICS or oral corticosteroids (Guilbert et al., 2014). Although most recent studies reported good tolerability of LABA therapy, its initial usage is still not recommended by the GINA report for pediatric patients. However, recent guidelines for the management of pediatric asthma, issued by the Saudi Initiative for Asthma (SINA), endorsed the early addition of LABA in combination with ICS therapy, due to evidence of confirmed positive outcomes, including the reduced incidence and severity of asthma exacerbations, and improved lung function (Al-Moammary et al., 2019).

The main adverse effects reported in most studies were attributed to corticosteroid therapy. These effects frequently occurred in patients with uncontrolled severe asthma symptoms, who required high-dose ICS or systemic corticosteroids for the management of the asthma exacerbations. A recent study indicated that asthma patients, treated with high-dose ICS, had more serious asthma-related events, compared with low-dose ICS, with or without LABA (Weinstein et al., 2019).

It is evident that additional research is required to evaluate and optimize the LABA/ICS combination therapy in pediatric patients, to reduce the incidence and severity of asthma exacerbations and to avoid the need for high ICS doses or systemic corticosteroids. This approach will reduce the morbidity and mortality associated with asthma exacerbations.

5. Limitations

One of the study limitations is the retrospective design, and including only patients admitted to the ED. We did not consider children with severe asthma admitted to the respiratory service through ambulatory care clinics for the management of asthma exacerbation or children received care for exacerbation in another center. In addition, the medical records of potential participants were provided by the Data Management Department of the KAIMRC, based on the chronic diagnosis of "severe asthma" presented in the patient chart, and the admission diagnosis of "asthma exacerbation" provided by the ED physician upon admission. Although we confirmed the diagnosis by reviewing the patients' medical charts, it is possible that some eligible patients were not included because they were not initially diagnosed as such. Due to the retrospective design of the current study, we did not collect data related to diet, smoking, and social status, or prescribed doses, and other asthma medications such as Leukotriene inhibitors, inhaler anticholinergics, or IgG monoclonal antibodies which could be a confounder affecting the analysis.

6. Conclusion

There is insufficient evidence to support or oppose the efficacy and safety of the concomitant use of LABA with ICS in pediatric patients. The current study confirmed the substantial efficacy of the LABA/ICS combination therapy in reducing the incidence and severity of asthma exacerbations in children, compared to ICS alone. However, additional researches are required to assess the full potential benefits of LABA in a larger sample size.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. NIH classification of asthma exacerbation

	Symptoms and Signs	Initial PEF or FEV_1*	Clinical Course
Mild	Dyspnea only with activity	PEF $\geq$ 70 %	■ Cared for at home ■ Relief with inhaled SABA ■ Possible short course of oral steroid
Moderate	Dyspnea interferes with or limits usual activity	PEF 40–69%	■ Requires Clinic or ED visit ■ Relief from frequent inhaled SABA ■ Oral steroids: some symptoms last for 1–2 days with treatment
Severe	Dyspnea at rest; interferes with conversation	PEF < 40%	■ Requires ED visit and likely hospitalization ■ Partial relief from frequent inhaled SABA ■ Oral steroids: some symptoms last for > 3 days after treatment is begun ■ Adjunctive therapies are helpful

* Predicted or personal Best

ED, emergency department; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; SABA, short-acting beta2-agonist

The table is adapted from the national heart, blood, and lung institute expert panel report 3 (EPR 3): guidelines for the diagnosis and management of asthma. NIH publications no.09–4051, 2007.

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