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Efficacy and safety of the combination fluticasone propionate plus salmeterol in asthmatic preschoolers: An observational study

Dr. Elpis Hatziagorou^a, Mrs. Eleana Kouroukli^a, Mrs. Maria Galogavrou^a, Mrs. Dafni Papanikolaou^a, Dr. Despoina Terzi^a, Dr. Pinelopi Anagnostopoulou^a, Fotios Kirvassilis MD^a, Demosthenes B Panagiotakos ^b, and John Tsanakas^a

^aAristotle University of Thessaloniki, Greece, Paediatric Pulmonology Unit, Hippokration Hospital, Thessaloniki, Greece; ^bHarokopio University, School of Health Science and Education, Athens, Greece

ABSTRACT

Background: Inhaled Corticosteroids (ICS) are the cornerstone of asthma management in pediatric patients. However, in some cases, asthma is not adequately controlled on ICS alone. Long-acting beta₂-agonists (LABA) are one of the available additional therapies but their use has rarely been studied among children younger than 5 years. **Objective:** The aim of this observational study was to evaluate the efficacy and safety of the combination of fluticasone propionate and salmeterol (FP/SA) in asthmatic children younger than 5 years of age. **Methods:** A retrospective study of 796 children under the age of 5 years (2.87 ± 1.22 years, 64.2% males), who were treated with FP/SA was conducted. Hospitalization rates, frequency of wheezing, exercise induced asthma, nocturnal wheeze and drug-related side-effects were recorded through children's medical records. **Results:** The children had previously received short-acting β_2 -agonists (73%), ICS (17%), montelukast (1%), and ICS with montelukast (2%). Mean duration of therapy with FP/SA was 12.45 ± 9.14 months. After adjusting for age, gender, and duration of treatment, a 89% reduction was recorded in annual hospitalization rates (from 27.13% before treatment to 3.01% after FP/SA therapy, $p < 0.001$), a 71% reduction in incidence of exercise-induced asthma (36.8% vs. after 10.6%, $p < 0.001$), a 81% reduction in nocturnal asthma (33.7% vs. after: 6.4%, $p < 0.001$), as well as in frequency of wheezing ($p < 0.01$). No previous treatment carry-on effect was observed. No major drug-related side-effects occurred in the study group. **Conclusions:** Combination therapy (FP/SA) is well-tolerated and highly effective in asthmatic children under the age of 5 years.

ARTICLE HISTORY

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KEYWORDS

Asthma; children; inhaled corticosteroids with long-acting beta₂-agonists

Abbreviations

EIA	Exercise induced asthma
FP/SA	Fluticasone propionate and salmeterol
GINA	Global Initiative for Asthma
ICS	Inhaled Corticosteroids
IMT	Initial maintenance treatment
LABA	Long-acting beta ₂ -agonists
NA	Nocturnal asthma
RCTs	Randomized Control Trials
SABA	Short-acting β_2 -agonists

Introduction

Asthma is the most common chronic disease among children (1) and its onset usually occurs early in childhood; around 25% of children with persistent asthma develop their first symptoms by 6 months and 75% by 3 years of age (2). Overall, up to 80% of children with asthma present with the condition before their fifth year of life

(3) while asthma is more prevalent in preschoolers than in any other age group (4). In addition, symptoms and clinical manifestations of asthma in this age group vary significantly among individuals, in regard to frequency and severity, triggering factors and symptom burden between wheezing exacerbations, rendering asthma particularly difficult to diagnose in preschoolers (5,6). Distinct wheezing phenotypes have been proposed as a means of classification (7,8), always with the aim of deciphering which children will benefit the most from maintenance treatment with ICS or other medications (2). However, the unique characteristics of this group, as well as the scarcity of trials involving children younger than 5 years often pose a great challenge in the selection of the optimal regimen (9–11).

Inhaled corticosteroids (ICS) are the cornerstone of asthma management and have been proven to be the most effective long-term treatment for this condition (11). The majority of children with asthma are adequately

controlled on low-medium doses of ICS but unfortunately, asthma symptoms often persists despite receiving the adequate ICS regimen. In such cases it is recommended to check for non-adherence and poor technique should then proceed to a step-up in the treatment plan (12). Long-acting β_2 -agonists (LABAs) are among the medications that can be used in combination with ICS, as an alternative to increasing the dose of ICS. The combination of ICS and LABAs has demonstrated benefits in lung function, symptom control and prevention of exacerbations, both in adults and children (13). However, the administration of LABAs has been studied only inconsistently in children younger than 11 years, and not at all in children younger than 4 years (3,14), apart from a few retrospective studies with small number of patients (4,15). Therefore, data concerning this age group are mainly extrapolated from studies in older children and LABAs have not been approved for use in children younger than 4 years (3). Additionally, the use of LABAs has been controversial over the years and associated with an increased risk of asthma-related adverse effects, such as life threatening pulmonary exacerbations (16). Nevertheless, some of the current guidelines hesitantly suggest the combination of a LABA with a ICS regimen, when sufficient asthma control has not been achieved (3,17). Recent guidelines on asthma treatment shift the focus to asthma control, rather than severity (18–20). Most researchers highlight the importance of an individualized approach when it comes to inadequately controlled asthma (12,20,21).

Based on the long-term clinical observations, in our specialized outpatient clinic, that direct response to ICS (FP) with a LABA (SA) leads to good asthma control, increased compliance and subsequently step down maintenance treatment to ICS, the aim of this study was to evaluate the efficacy and safety of the combination of an ICS (FP) with a LABA (SA). To test the research hypothesis, medical records from a large cohort of preschoolers with poorly controlled asthma in a real-life setting were retrieved and compared to historical controls' data (22–26).

Methods

Study design

We conducted a retrospective, observational, single-center study, based on the medical records of 796 children under the age of 5 years with moderate–severe asthma, who had received the combination FP/SA as monotherapy chronic treatment for their asthma. All children included in the study were monitored in the Outpatient Asthma Clinic of the Paediatric Pulmonology Unit of Hippokration General Hospital of Thessaloniki, a tertiary

care center. Patient selection took place from December 2002 to April 2015.

Study sample

This study included 796 children (64.2% male) under the age of 5 years, who had received the combination FP/SA as maintenance treatment for their asthma. The inclusion criteria comprised: 1) age younger than 5 years, 2) a diagnosis of moderate-severe asthma according to the GINA criteria (14) and 3) a minimal duration of FP/SA treatment of 3 months, i.e., patients were eligible for the study if the treatment was initiated before their fifth birthday and continued for at least 3 months (3 months of consecutive prescriptions).

Procedures

The daily dose of FP was 200 μ g, administered twice daily with 2 puffs of FP/SA 50/25 μ g, through a metered-dose inhaler with aerochamber and mask. All patients used short-acting β_2 -agonists for immediate relief of symptoms when needed over the study period. Any previous and concomitant asthma medication during the last 3 months before enrollment was recorded but did not serve as an exclusion criterion. The endpoint of monitoring was set as either the end of treatment with FP/SA because of clinical improvement allowing for a step-down in therapy, or the day the patients turned 5 years old, whichever occurred first. Exclusion criteria included cardiac co-morbidities, or other chronic diseases.

Efficacy and safety assessment

Children were followed every three- four months in the asthma clinic and parents were asked based on a standardized questionnaire on the number of hospitalizations had, the frequency of cough and wheeze episodes, exercise induced asthma (EIA), nocturnal asthma (NA) and potential medication-related adverse events over the last three months. Inhaler technique was checked in every visit. Efficacy was evaluated with the changes in: (a) hospitalization rates, (b) frequency of cough and wheeze, (c) exercise induced asthma (EIA) and (d) nocturnal asthma (NA), one year before and one year after the initiation of treatment. Regarding the frequency of symptoms, patients were categorized into 4 groups; less than 2 episodes of cough or wheezing per year, less than 6 episodes per year, less than 2 episodes per week and more than 2 episodes per week. The safety of the treatment was assessed by recording any adverse events (asthma, respiratory, cardiovascular serious adverse events, or any other adverse events) that occurred during the study period.

Ethics

The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Aristotle University of Thessaloniki. Data were obtained from patients' medical records.

Statistical analysis

Descriptive statistics (mean, standard deviation and frequencies) were used to present children's characteristics and incidence rates. Incidence rates comparisons were performed using the McNemar chi-squared test. Generalized Estimating Equations (GEE), a procedure that extends the generalized linear models to allow for analysis of repeated measurements, were used to evaluate rates of hospitalizations and the other outcomes in relation to children's age, gender, and duration of treatment. Two-level repeated measurements were used (before and after the initiation of FP/SA treatment), with the dependent outcomes being under the binomial distribution and the parameter estimates derived using the maximum likelihood method. Since no control group was available in this work, historical controls' data were retrieved from the literature (22–26). Comparisons were performed again using GEE, but with fixed values for the studied response outcomes. Level of significance was set to $p < 0.05$. Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS Statistics 20, IBM Hellas Inc.).

Results

The mean age of children was 2.87 ± 1.22 years; 64.2% were males. Age distribution is shown in Figure 1. The distribution of the previous medication that children had received was short-acting β_2 -agonists (SABA) (73%), ICS plus SABA per needed (17%), MON plus SABA per needed (1%) and MON plus ICS plus SABA per

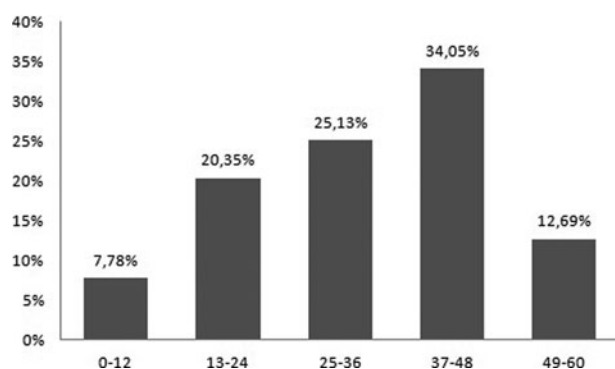


Figure 1. Age distribution of the patient population (months).

Table 1. Characteristics and asthma medication use of the study population. Results are presented as N (%), or Mean (SD).

Characteristics	N (%) or Mean $\pm$ SD
N	796
Sex, male (%)	511 (64.2)
Age (years)	2.87 ± 1.22
Duration of treatment (months)	12.45 ± 9.14
Prior medication use (%)	
None	57 (7)
Salbutamol	584 (73)
Montelukast sodium	5 (1)
Inhaled corticosteroids	135 (17)
Inhaled corticosteroids + Montelukast sodium	15 (2)

needed (2%), while 57 children (7%) did not receive any treatment (Table 1).

Efficacy

The mean duration of monotherapy with FP/SA was 12.45 ± 9.14 months. After the initiation of FP/SA treatment, the annual rate of hospitalizations was significantly reduced by 89% (before: 27.13% vs. after: 3.01%, $p < 0.001$) (Figure 2); and this reduction was independent of children's age, gender and duration of therapy. Frequency of wheezing (daily, weekly, monthly or yearly) was also reduced ($p < 0.01$). Specifically, before the start of FP/SA treatment, 59.5% of the patients presented exacerbations weekly and 34.2% every two months, whereas, one year after the initiation of combination treatment, 48.7% of the children presented episodes of wheezing every two months and 37.5% twice per year (Figure 3). The incidence of exercise induced asthma (EIA) decreased by 71% (before: 36.8% vs. after: 10.6%, $p < 0.001$). Similarly, the incidence of nocturnal asthma (NA) decreased by 81% (before: 33.7% vs. after: 6.4%, $p < 0.001$) (Figure 4). As for the case of hospitalizations,

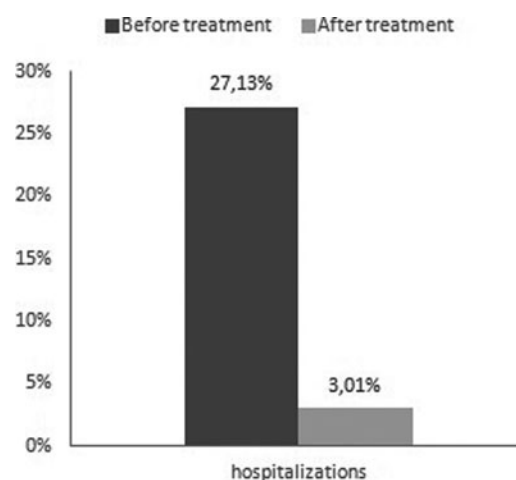


Figure 2. Significant reduction of hospitalizations was recorded one year after initiation of treatment ($p < 0.001$).

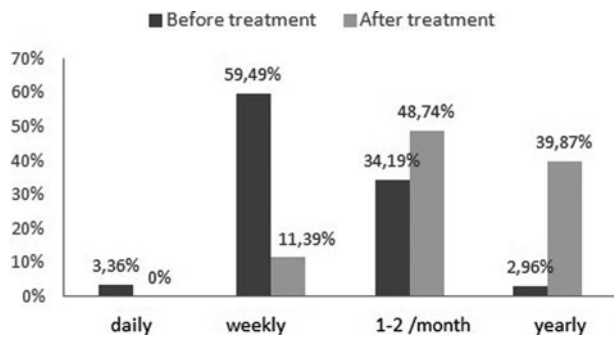


Figure 3. The frequency of wheeze was significantly reduced one year after initiation of FP/SA therapy ($p < 0.01$).

the aforementioned reductions in asthma episodes were independent of children's age, gender and duration of therapy. Using historical data retrieved from the literature with other medications it was revealed that the hospital readmission rates observed among children receiving FP/SA treatment in our study was significantly lower as compared to the historical data (i.e., vs. hospital readmissions varied from 1.4% to 18.0%, $p = 0.012$); similar results were observed as regards incidence of EIA (i.e., vs. EIA varied from 23% to 63%, $p < 0.001$), and NA (i.e., vs. NA varied from 20% to 60%, $p < 0.001$).

The analyses were repeated by the type of previous medication children received, in order to evaluate a potential carry-on effect of past medication. For children previously receiving SABA, the hospitalizations rates reduced by 89% (before: 22.6% vs. after: 2.5%, $p < 0.001$), incidence of EIA reduced by 73% (before: 47.2% vs. after: 12.8%, $p < 0.001$) and incidence of NA decreased by 83% (before: 46.7% vs. after: 7.9%, $p < 0.001$). Similarly, for children previously receiving ICS plus SABA, hospitalizations rates reduced by 96% ($p < 0.001$), incidence of EIA reduced by 94% ($p < 0.001$) and incidence of NA reduced by 83% ($p < 0.001$). No differences were observed in the studied outcomes between children previously being under SABA treatment vs. ICS plus SABA

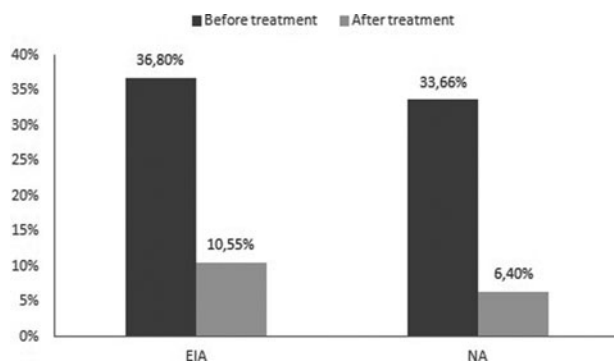


Figure 4. Exercise induced asthma (EIA) and Nocturnal asthma (NA) were significantly reduced one year after initiation of FP/SA, ($p < 0.01$).

(all p -values > 0.48). Since the number of children receiving MON plus SABA or MON plus ICS and SABA was very small no additional analyses were performed.

Side effects

No major side effects were observed in the studied children. Only 16 (2%) of the children reported moderate irritability and 5 (0.6%) hoarseness of voice.

Discussion

Our retrospective real-life study in a large cohort of asthmatic children under 5 years of age shows that the administration of combined FP/SA therapy is both safe and efficacious, resulting in significant reduction in hospitalization rates, frequency of wheezing (daily, weekly, or monthly), incidence of exercise-induced and nocturnal asthma ($p < 0.01$).

In the past, 2 large randomized controlled studies associated the use of LABAs with an increased risk of asthma fatality, as was shown by the comparison of the patient groups receiving salmeterol and salbutamol or salmeterol and placebo respectively (27,28). Both studies included a large but heterogeneous sample of patients over 12 years with asthma (including adults with chronic obstructive pulmonary disease – COPD), to whom SA was administered in a separate inhaler with the instruction to continue their previous treatment. Therefore, a possible explanation for the adverse outcome of these studies is that the bronchodilation and relief of symptoms following LABA administration may have led to poorer adherence or even discontinuation of the maintenance treatment (29,30), which subsequently led to the occurrence of uncontrolled exacerbations. Nonetheless, these studies do not provide concrete evidence of the safety of the FP/SA combination, and the patient sample examined therein is substantially different from preschool children, which are the focus of the present study.

On the contrary, subsequent studies, in which SA was administered as add-on therapy in asthmatic children receiving ICS, yielded favorable results. Two RCTs that included children older than 6 years (31,32) compared the efficacy of 3 different treatment step-up options, with FP being the cardinal treatment: addition of SA, addition of MON or doubling the dose of FP. In one study, the combination FP/SA was found equipotent to ICS monotherapy (31), while the other study found the combination to be more effective (32). Two more RCTs published in 2009 confirmed the hypothesis of non-inferiority of the FP/SA combination compared to doubling the dose of FP in children older than 4 years with asthma not controlled on standard doses of ICS (20,33). These studies noted

that ICS/LABA combination treatment might improve patient adherence and allow satisfactory asthma control to occur on lower doses of ICS, which is of particular importance in children. A subsequent RCT that included younger patients (4–7 years old) examined the efficacy of FP/SA as compared to FP monotherapy and found that children who received the combination FP/SA saw a greater improvement in lung function, while the incidence of adverse effects was equally low in both groups (34). Finally, 2 recent large RCTs examined the safety of the FP/SA combination, one in adults and adolescents older than 12 years (35), and the other in children aged 4–11 years (36). Neither study found an increased risk for serious events in the SA group, while the pediatric study concluded that the combination of ICS and SA may have a protective effect on asthma exacerbations, but a statistically significant difference from the ICS monotherapy group was not detected.

In an elegant, retrospective, multicenter study of 50 patients under the age of 5 years treated with FP/SA, Sekhsaria et al analysed changes in emergency room visits, hospitalization rates, frequency of wheezing and the impact on growth, by interpreting the change in height percentiles, and they were able to demonstrate that FP/SA is both efficacious and safe in this age group (4). Although the results reported in the study by Sekhsaria et al are of great interest, it is likely that their impact may be somewhat blunted by the relatively small number of patients involved. The findings of our study, involving 796 children younger than 5 years are in keeping with those previously described by Sekhsaria et al. Moreover, our study demonstrated significant improvement/reduction in the incidence of exercise-induced asthma and nocturnal asthma as well.

Strengths and weaknesses

Although retrospective in nature, our study included a very large sample of preschool children with moderate-severe asthma and can therefore provide valuable insight into the real-life responses (safety and effectiveness) of this particular group to FP/SA combination treatment.

A well known limitation of observational or pre-post studies of asthma treatment is the substantial improvement in patients over time that may reflect either the expected improvement in symptoms over time in pediatric asthma. Besides, this was a retrospective study; there was no control group receiving only ICS. A prospective study is necessary to further compare safety and effectiveness of the combination of FP/SA to ICS alone. In order to balance these limitations, we compared the results from our large cohort of preschoolers with poorly controlled asthma to historical controls' data. Using historical data

retrieved from the literature with other medications it was revealed that the hospital readmission rates, EIA and NA observed among children receiving FP/SA treatment in our study were significantly lower as compared to the historical data (22–26).

Interestingly, the vast majority of the children included in this study (81%) were steroid-naïve, in the sense that they received the combination as initial treatment for their asthma. This practice contradicts all existing guidelines regarding the treatment of asthma in this age group, according to which only 19% of the children included in this study would be entitled to a therapeutic trial with FP/SA. However, recent guidelines concerning the selection of the appropriate treatment for asthma shift the focus to asthma control, rather than severity (18–20), given that poorly controlled symptoms are an accurate predictor of exacerbations (19). An integrated data analysis of 4 RCTs attempted to identify a set of GINA-defined asthma features that correlate with an anticipated favorable response to initial maintenance treatment (IMT) with FP/SA, rather than ICS monotherapy (18). Patients were assessed on the basis of 3 baseline features of uncontrolled asthma: moderate-severe airflow limitation, daily symptoms and daily use of reliever medication. The results demonstrated that those who exhibit 2 or 3 of those features are significantly more likely to achieve better control with IMT with SA/FP than with FP alone, and the benefit was greater in patients who exhibited all 3 features. The analysis included patients 12 years and older, and therefore some of the features used to define the level of asthma control in these patients are not completely in line with the age-specific criteria used for the same purpose in preschoolers (e.g. assessment of airflow limitation through spirometry is not applicable in most children younger than 5 years). Nevertheless, children included in the present study were referred to our specialized unit precisely because they exhibited various indicators of poorly controlled asthma (weekly symptoms, EIA, frequent use of rescue medication and NA) (14), and therefore a therapeutic trial with SA/FP was deemed appropriate and more likely to provide a satisfactory response. This was a real-life study based on our experience indicating better response to IMT with FP/SA, rather than ICS monotherapy. Besides, in order to balance this limitation, the analyses were repeated by the type of previous medication children received, in order to evaluate a potential carry-on effect of past medication. No differences were observed in the studied outcomes between children previously being under SABA treatment vs. ICS plus SABA (all p-values > 0.48).

Most researchers highlight the importance of an individual approach when it comes to inadequately controlled asthma requiring a step-up in the treatment plan, since

the best option for these patients has not yet been defined or supported by concrete evidence (12,20,21). LABAs should in no way be used as a monotherapy (10) or undermine the importance and proven benefits of ICS treatment. However, they may constitute a valuable option for enhancement of the therapeutic regimen. Given the age-specific challenges of asthma management in preschoolers, we argue it is imperative that additional and alternative treatment options are explored, and eventually incorporated in the guidelines, especially for patients with inadequate response to ICS. We hope that our study will act as an incentive for re-examination of safety issues associated with LABAs and further research in this challenging and highly demanding group of patients.

Conclusions

The incidence of asthma is higher in children younger than 5 years than it is in any other age group; however, the data and evidence concerning these patients are limited and mainly inconsistent, since only a few retrospective studies have included children younger than 4 years of age (4,15). Furthermore, children who present with uncontrolled asthma or children whose asthma is not sufficiently controlled on ICS are commonly a source of confusion for caregivers. The combination of ICS and LABAs are among the available treatment options for asthma, but they have not been adequately studied in such young patients and therefore, they are not officially recommended in the current age-specific guidelines. In this retrospective study, the FP/SA combination was found to be both safe and effective in children younger than 5 years. The favorable results of recent studies should serve as an incentive to re-examine safety issues associated with ICS/LABA combination treatment, as well as to consider the incorporation of LABAs in the current guidelines for asthma management in preschool children.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Ethics approval

Hippokration Hospital Ethics Committee approval.

Contributors

EH, DBP and JT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EH, FK and JT contributed substantially to the study design, data analysis and interpretation. DBP and EH performed the statistical analysis. EK, DP, DT and PA collected all retrospective data of the study. All the authors contributed

to the writing of the manuscript. EH, EK, DBP and JT reviewed and edited the manuscript. EH and JT are guarantors.

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ORCID

Demosthenes B Panagiotakos  <http://orcid.org/0000-0001-8583-153X>

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