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# A Pilot Study of Daily Fluticasone Propionate and Episodic Salmeterol/ Fluticasone Propionate in Childhood Asthma

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## Abstract

**Background:** A corticosteroid inhaled (ICS) daily is recommended by medical experts for patients with persistent asthma who need to use an asthma controller. However, due to the inconvenience of this method, some children in Thailand may receive episodic inhaled corticosteroid.

**Objective:** To compare the efficacy of fluticasone propionate inhaled (IFP) daily and salmeterol/fluticasone propionate inhaled (ISFP) episodically in children with mild asthma.

**Methods:** Seventy-two children aged 14 to 121 months (mean age = 53.76 months) with recurrent wheezing and asthmatic tendencies participated in the study. The participants were randomly selected to receive either a daily IFP (N=34) or a 14-day course of treatment with ISFP starting with the onset of symptoms (N=38). The primary outcome under investigation was the number of exacerbations requiring treatment with a systemic corticosteroid and the secondary outcome observed was the increased height among the participants and safety of using combined salmeterol/fluticasone propionate. A proportional-hazards regression model and ANOVA were used for statistical analysis.

**Results:** Six months post-treatment, the percentage of exacerbations which needed systemic corticosteroids between the two groups had no significant differences ($p=0.186$). The median height increased from baseline also had no significant differences ($p=0.565$). The median cumulative ICS dose in the daily IFP group (45,000 mcg) and the episodic ISFP group (7,000 mcg) was significantly different ($p<0.001$). No adverse events were found in the episodic ISFP group.

**Conclusions:** There were no significant differences in reducing exacerbations and height suppression between the daily IFP and episodic ISFP groups in the six-month study period.

**Keywords**: Asthma; Wheezing; Child; Inhaled Corticosteroid; Fluticasone Propionate; Salmeterol

## Introduction

Asthma is the most common chronic airway inflammatory condition in children and adults worldwide. Recently, the prevalence of this disease and other atopic diseases tend to increase. The increased cost in terms of treatment and sick leave will be a burden to patients and their families [1, 2].

When patients are exposed to multiple triggers, i.e. sensitized allergens, pollutants, cold, exercise, and infections, their airways become hyper-responsive and constrict. The bronchospasm in asthmatic patients presents as dyspnea and wheezing on auscultation. In severe cases, patients have further inflammation and prolonged asthmatic exacerbation. If the inflammation happens repeatedly or becomes chronic, patients may have airway remodeling or irreversible fixed airflow obstruction. Thus, early diagnosis and treatment are necessary to prevent airway damage and improve patient lung functions. However, diagnosing pediatric asthma is difficult, especially in preschool children, due to atypical presentations or mildness of symptoms. In addition, other diseases, like respiratory viral infections, have similar presentations of wheezing bronchi. Spirometry, the primary reliable test for asthma, is hard to perform on this age group [3]. Due to the uncertainty of asthma diagnoses in preschool children, the Global Initiative for Asthma (GINA) 2016 recommends using an inhaled corticosteroid or anti-leukotriene as a controller in children younger than five years of age who have more than three episodes of wheezing – particularly when they are precipitated by exercise, laughing, and/or crying for longer than 10 days, during respiratory tract infections, and those predisposed to atopic diseases (i.e. atopic dermatitis, food allergies, and/or family history of asthma in a first-degree relative) [3].

Following 2016-GINA guidelines, regular use of a daily inhaled corticosteroid (ICS) or anti-leukotriene is mandatory for patients with asthma and children with asthmatic tendencies (young children who have frequent episodes of wheezing and atopic disease of their own and/or asthma in a first-degree relative). This treatment is proven to reduce asthmatic symptoms, risks of asthma-related exacerbations, hospitalization, and deaths. For this reason, poor adherence may lead to a long-term cycle of worsening symptoms, increased exacerbations, and decreased lung functions. However, reality, long-term adherence may be not possible for many patients. Therefore, it is important to seek another effective but flexible treatment protocol apart from the daily use of a controller. Two prior studies compared the efficacy of daily ICS and intermittent ICS in controlling asthma. Papi conducted a three-month parallel randomized controlled study that concluded in children aged 12 to 28 months with acute exacerbations during upper respiratory tract infections, there were no significant differences in the rate of exacerbations per patient-year between the daily inhaled beclomethasone and intermittent inhaled beclomethasone treatment groups [4]. Similarly, a 52-week parallel randomized controlled study by Zeiger showed no significant differences in symptom-free days and positive asthma predictive index between daily inhaled budesonide and intermittent inhaled budesonide treatments in children aged 12 to 53 months with intermittent asthma or episodic viral-wheezing [5].

On the other hand, two later studies showed the superiority of daily ICS over intermittent ICS in asthmatic control and lung function improvement. In Chauhan's systematic review study, the intermittent ICS group displayed smaller improvement of PEFR, fewer symptom-free days, fewer asthma-controlled days, more use of rescue beta2-agonist, and greater increase in FENO from baseline compared to the daily ICS group [6]. Li demonstrated in a parallel randomized controlled study that daily ICS/LABA had significantly lower clinical symptom scores but higher PEF% and FEV1% when compared to the intermittent approach [7].
There are controversies and challenges with respect to the efficacy of daily ICS versus intermittent ICS in children with asthma or episodic viral-wheezing. Therefore, we aimed to examine the efficacy of symptom control between daily ICS and episodic inhalation of a fixed-dose combination of inhaled corticosteroids and a long-acting beta2-agonist (ICS/LABA) in children with asthma or frequent wheezing. This study also evaluated the safety of ICS/LABA in children with a history of recurrent wheezing and compared the growth of height in children from both groups.

## Materials and Methods

A six-month prospective, randomized, comparative study was performed in children aged fourteen to 121 months (mean age = 53.76 months) with a history of mild asthma or recurrent wheezing with asthmatic tendencies at the Allergy Division of the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok, Thailand. The participants were recruited from September 2016 to September 2017.

The inclusion criteria were children aged one to 15 years who had recurrent wheezing at least three times/year and presented at least two of five symptoms; coughed or wheezed more than 10 days during respiratory tract infection; had night worsening of symptoms; coughed or wheezed as a result of being triggered by exercise, laughing, and/or crying; had a history of atopy (i.e.atopic dermatitis, allergic rhinitis, or first-degree relatives with asthma) or asthma diagnosed using spirometry. We did not include children who were using either ICS or leukotriene receptor antagonists (LTRA) in the study.

All participants or their parents agreed to be involved in the study and provided written informed consent. The study was approved by the Child Health Ethics Committee of the Queen Sirikit National Institute and registered in the Thai Clinical Trials Registry (TCTR 20180614002).

Patients who met the criteria of mild asthma or tended to have asthma were randomly assigned to receive either 125 mcg of fluticasone propionate (IFP) MDI via a spacer twice daily or 25/125 mcg of salmeterol/fluticasone propionate (ISFP) via a spacer twice daily for 14 days during respiratory tract infection. All participants received 100 mcg of salbutamol MDI (2-6 puffs) via a spacer during asthmatic exacerbations. All comorbidities were treated following the standard clinical practice guidelines. Check-ups were conducted at the QSNICH Allergy Clinic at one, three, and six months, post-enrollment for asthma symptom control, proper inhaler usage, and growth assessment. The medication adherence was exclusively monthly check-up by telephone call. In the second, fourth, and fifth month, the participants were interviewed by phone to assess symptom control and medication adherence. The primary outcomes were the efficacy of inhaled fluticasone versus the combination of salmeterol/fluticasone propionate in terms of the percentage of symptom control, time to first asthma exacerbations requiring systemic corticosteroids, and wheezing-related hospitalization. The secondary outcomes were the increase in height over the six-month study period and the safety of salmeterol/fluticasone propionate in children with recurrent wheezing.

The participants presenting with 1) continuously uncontrolled disease for three months, 2) severe wheezing requiring more than two times of hospitalization, 3) severe wheezing requiring intubation, and 4) severe exacerbations requiring ICU admission were dropped from the study.

### Statistical Analysis

The data were recorded and analyzed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL, USA). The descriptive data were analyzed using the Mann-Whitney U test and the Fisher's exact test. A univariate analysis adjusted by age was used for continuous variable outcomes. The Mann-Whitney U test was used for categorical variable outcomes. The proportional-hazards regression model was used for time-to-event outcomes.

## Results

Seventy-two children were enrolled in the study with details as presented in Figure 1. Sixty-two children (86.1%) completed the six-month follow-up. Ten children were excluded from the study due to incomplete data. Seven did not complete the follow-up (four in the daily IFP group and three in the episodic ISFP group). Among the patients in the episodic ISFP group who did not complete the study, two withdrew consent, and one used another controller during the study period. Thirty children in the daily IFP group and 32 in the episodic ISFP group completed the study. The demographic data and baseline characteristics are shown in Table 1. There were no statistically significant differences between the two groups.

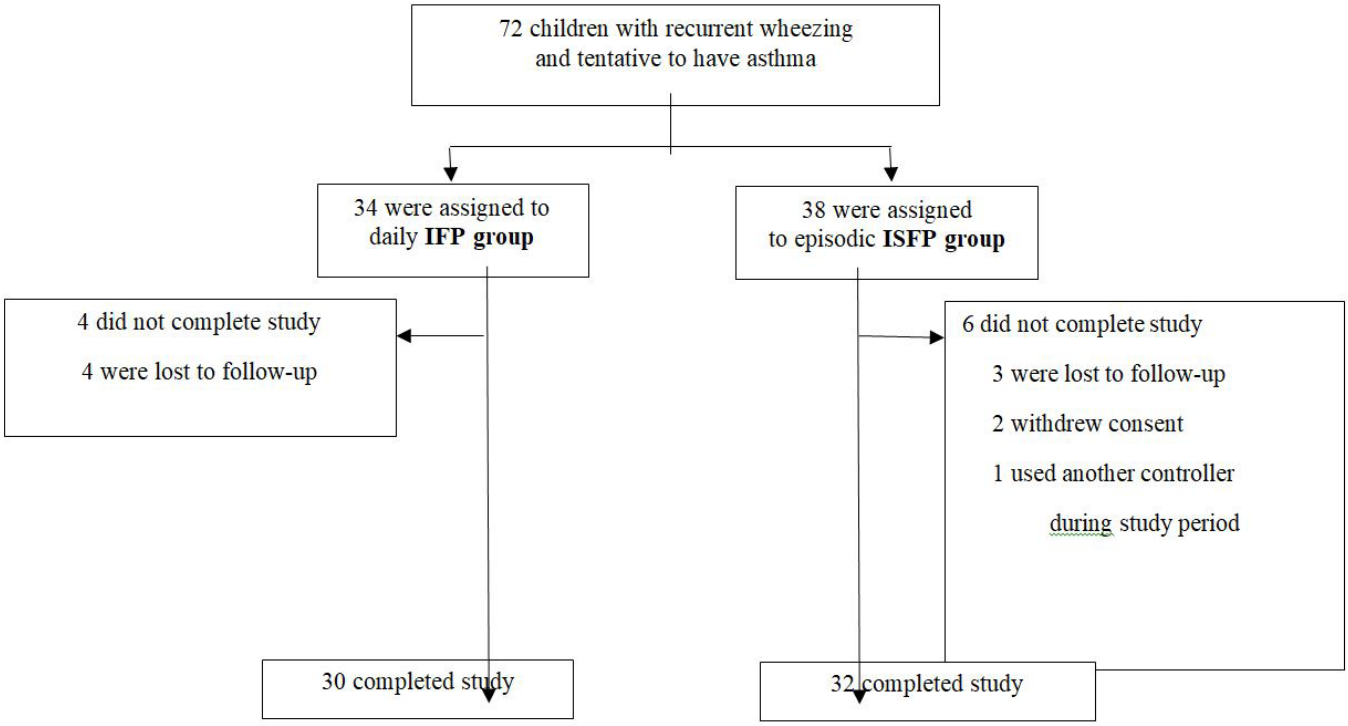



**Figure 1:** Study Design and Enrollment

**Table 1:** Demographic Data and Baseline Characteristics

| Characteristics | Total (N = 62) | Daily IFP (N = 30) | Episodic ISFP (N = 32) | p-value |
|---|---|---|---|---|
| Age 12-60 months – no. (%) | 39 (62.9) | 16 (53.3) | 23 (71.9) | 0.189 |
| Male – no. (%) | 43 (69.4) | 20 (66.7) | 23 (71.9) | 0.785 |
| C/S birth method – no. (%) | 31 (50) | 16 (53.3) | 15 (46.9) | 0.800 |
| Birth weight (grams) – median (IQR) | 3000 (2750, 3300) | 3000 (2800, 3230) | 3000 (2600, 3350) | 0.646 |
| BMI (kg/m$^2$) – median (IQR) | 15.3 (14.4, 17.6) | 15.1 (14.2, 16.9) | 16 (14.4, 18.2) | 0.210 |
| No. of wheezing episodes in past year – median (IQR) | 3 (3-5) | 3 (2, 5) | 3.5 (3, 5) | 0.730 |
| Tobacco smoke exposure – no. (%) | 35 (56.5) | 16 (53.3) | 19 (59.4) | 0.798 |
| Aeroallergen sensitization – no. (%) | 45 (72.6) | 22 (73.3) | 23 (71.9) | 1 |
| Blood eosinophil ≥4% – no. (%) | 4 (6.5) | 2 (6.7) | 2 (6.3) | 1 |
| Eczema – no. (%) | 25 (40.3) | 13 (43.3) | 12 (35.7) | 0.796 |
| Allergic rhinitis – no. (%) | 56 (90.3) | 29 (96.7) | 27 (84.4) | 0.197 |
| Adenoid hypertrophy – no. (%) | 4 (6.5) | 0 (0) | 4 (12.5) | 0.114 |

| Characteristics | Total (N = 62) | Daily IFP (N = 30) | Episodic ISFP (N = 32) | p-value |
|---|---|---|---|---|
| Obesity – no. (%) | 5 (8.1) | 1 (3.3) | 4 (12.5) | 0.355 |
| Sinusitis – no. (%) | 2 (3.2) | 1 (3.3) | 1 (3.1) | 1 |
| Gastroesophageal reflux – no. (%) | 1 (1.6) | 0 (0) | 1 (3.1) | 1 |
| Parenteral asthma – no. (%) | 13 (21) | 4 (13.3) | 9 (28.1) | 0.215 |
| Month of index date – median (IQR) | 11 (3, 12) | 10 (2, 11) | 11 (3, 12) | 0.195 |

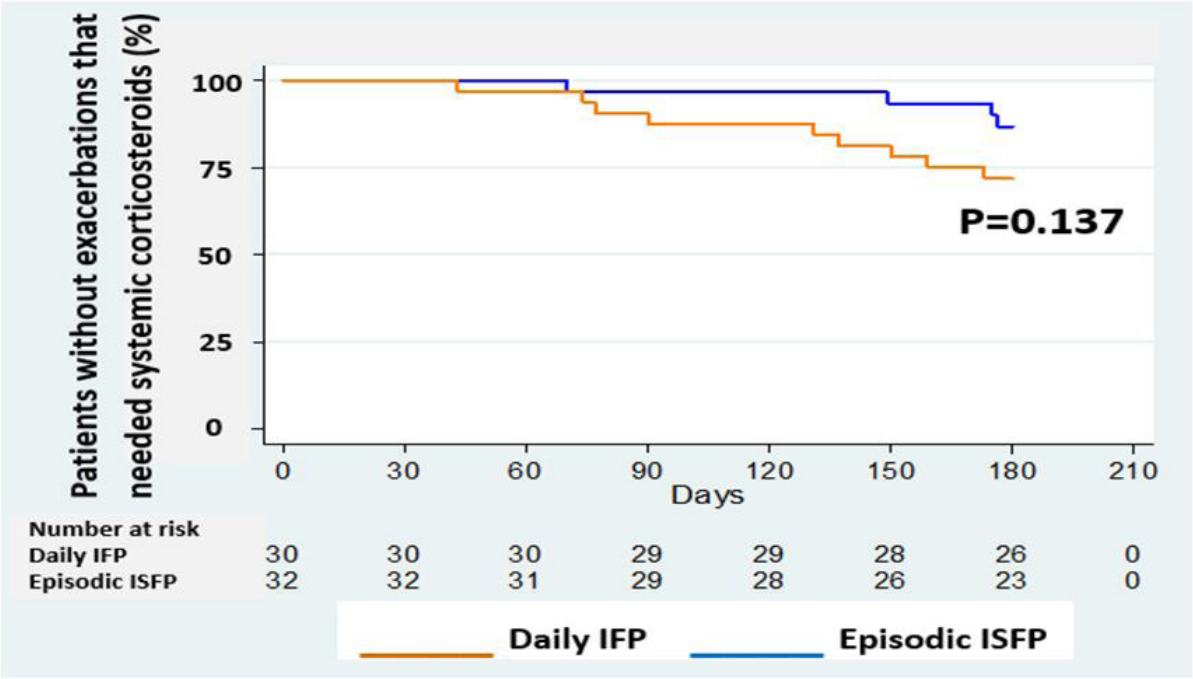
(P-value corresponding to the Mann-Whitney U test and the Fisher's exact test)

The cumulative doses of inhaled fluticasone propionate at six months in the daily IFP group was significantly different from those in the episodic ISFP group (45,000 mcg and 7,000 mcg respectively at $p<0.001$). The primary outcomes, the frequency and time to first exacerbations requiring systemic steroids, wheezing-related healthcare utilization, hospital admissions, days of admission, and symptom-free days were assessed for the efficacy of symptom control. The frequency and time to first events between the two groups had no statistically significant differences (Table 2 and Figure 2A, 2B, and 2C). The secondary outcomes (the rate of growth in height at month six = 4 cm, both groups) between the two groups had no statistically significant differences (p-value = 0.565). No serious asthma-related adverse events resulted from using the inhaled salmeterol/fluticasone propionate in children aged one to 15 years with recurrent wheezing. The hypopigmented skin surrounding the face mask contact area was the only side effect found in patients using inhaled corticosteroids (n=1, p-value = 0.274). There were no other side effects found in the rest of the patients.

**Table 2:** Outcomes at month six

| Outcomes | Total (N = 62) | Daily IFP (N = 30) | Episodic ISFP (N = 32) | p-value |
|---|---|---|---|---|
| No. of exacerbations requiring systemic corticosteroids – no. (%) | 13 (21.0) | 4 (13.3) | 9 (28.1) | 0.186 |
| No. of wheezing-related health care utilizations – no. (%) | 16 (25.8) | 7 (23.3) | 9 (28.1) | 0.736 |
| No. of hospital admissions – no. (%) | 5 (8.1 | 2 (6.7) | 3 (9.4) | 0.767 |
| Days of hospital admissions – median (IQR) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.746 |
| Episode free days – median (IQR) | 178 (176, 180) | 179 (176, 180) | 177 (175.5, 179) | 0.086 |

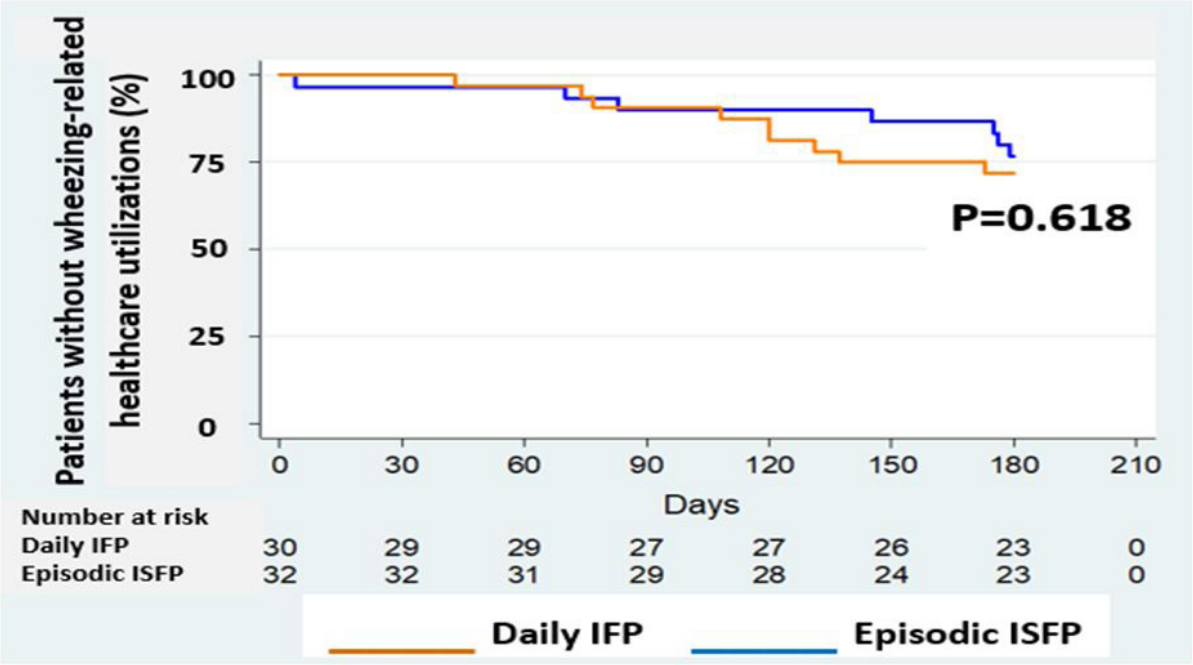
(P-value corresponding to the univariate analysis after age adjustment)




A hazard ratio of 2.38 (95% CI: 0.733 to 7.740)

(P-value corresponding to the proportional-hazards regression model)

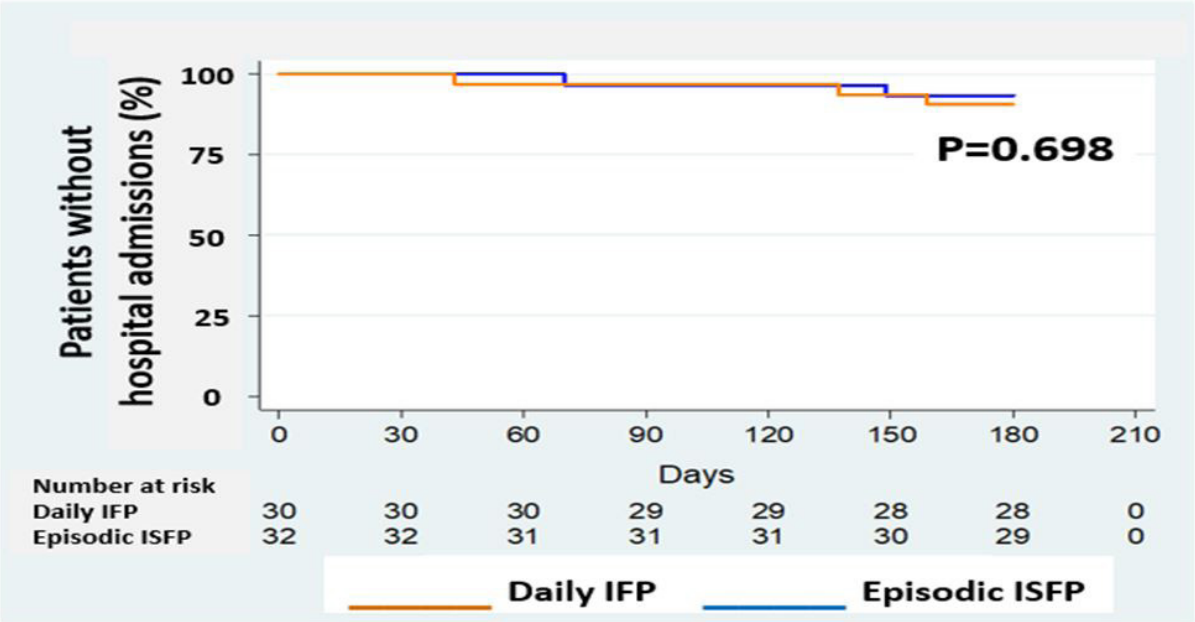
**Figure 2A:** Frequency and time to first exacerbations requiring systemic corticosteroids




A hazard ratio of 1.29 (95% CI: 0.48 to 3.45)

(P-value corresponding to the proportional-hazards regression model)

**Figure 2B:** Frequency and time to first wheezing-related healthcare utilization




A hazard ratio of 1.42 (95% CI: 0.24 to 8.51)

(P-value corresponding to the proportional-hazards regression model)

**Figure 2C:** Frequency and time to first hospital admissions

## Discussion

The Global Initiative for Asthma (GINA) recommends using daily inhaled corticosteroids as a controller in asthmatic patients for disease control and airway-remodeling prevention. Nevertheless, there may be inconsistencies in patient adherence. In practice, few patients strictly follow the daily controller protocol. This may stem from unawareness of disease outcomes or concerns over the side effects of steroid. Hence, we attempted to find an alternative treatment for controlling asthma.

Previous studies showed fewer benefits from treatment with an intermittent higher dosage controller over daily ICS. Papi and Zeiger reported no superior outcomes of a high dosage of intermittent inhaled corticosteroids over a low daily dosage in asthma control [4, 5]. Chauhan also demonstrated an intermittent ICS treatment is less effective than daily ICS (e.g. smaller improvement of PEFR, fewer symptom-free days, fewer asthma-control days, more use of a rescue beta2-agonist, and greater increases in FENO from baseline) [6]. However, these results may differ for a combination of an inhaled long-acting beta2 agonist and corticosteroid treatment. Li demonstrated intermittent inhaled salmeterol/ fluticasone propionate (SM/FP) showed similar treatment results to daily SM/FP in FEV1% increase ($p<0.05$) at month six but not at month 12 [7]. Thus, this advantage might not be long-lasting. Sposato suggested that adult patients receiving regular ICS plus LABAs did better than with intermittent treatment in controlling their asthma over a four-year follow-up period. However, after four years, the patients in both groups had similar declines in lung functions [8].

In short, the combination of inhaled LABA presented better outcomes than inhaled ICS alone, as shown in many previous studies. These studies suggest a stronger decrease in the severe exacerbation rates among patients receiving a fixed dose of inhaled LABA and corticosteroids than those receiving inhaled corticosteroids alone [9-11].

Our study is arguably the first to compare the efficacy of a daily medium dose of inhaled fluticasone propionate with that of a 14-day course of inhaled salmeterol combined with a medium dose of fluticasone propionate during respiratory tract infection in children with asthmatic tendencies or predispositions. The results of this study show that children treated with episodic ISFP have similar six-month outcomes as those treated with a daily IFP in exacerbation reduction, wheezing-related healthcare utilization, and hospital admissions.

Apart from good efficacy, we also found no side effects for intermittent ISFP, which is in concordance with Yoshihara's study showing the benefits of treatment with inhaled salmeterol (50 mcg/day) combined with fluticasone propionate (100 mcg/day) in treating childhood asthma for 12 weeks. This treatment improved nighttime sleep disorder scores with no safety concerns in children with asthma aged six months to five years [12].

As for the children's growth in height measured at months one, three, and six for all participants in both study groups, differences were not found. At month one after treatment, the height increase of children in the episodic ISFP group was significantly higher than that in the daily IFP cohort. However, by six months, there were no differences from baseline between the two groups, which also concords with Yoshihara [12]. In addition, Lone found that although the growth rates of asthmatic children who received long-term treatment with budesonide were significantly reduced during the first years of treatment, these changes were not significantly associated with final adult height [13]. However, Kelly and Loke suggest that long-term use of inhaled corticosteroids in asthmatic children would lower the attained height rate and their adult height compared to non-ICS users [14, 15]. We suggest that longer follow-up periods may show a different outcome.

Despite presenting insights into effective alternative treatments for children with recurrent wheezing, the present study has some limitations. First, it is a single-center study with weak power. Regarding to the results on the first half of our study ($p_1 = 0.281$, $p_2 = 0.133$), the total participants should be 260 children to make enough power to show the difference between 2 groups following the primary outcome. The calculation of sample size is based on this formula.

$$n_{trt} = \left[ \frac{z_1 - \frac{a}{2}\sqrt{\overline{pq}\left(1+\frac{1}{r}\right)} + z_1 - \beta\sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(outcome|treatment), q_1 = 1 - p_1$$

$$p_2 = p(outcome|control), \quad q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1 + r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{con}}{n_{trt}}$$

Secondly, the follow-up period may not be long enough to see any long-term effects of the treatment. Our suggestions for further comparative efficacy studies include increasing the sample size, having a longer follow-up period, adding daily ISFP and intermittent IFP as control groups to see treatment effects more clearly, and monitoring pulmonary functions in young children to evaluate treatment efficacy.

## Conclusions

There were no significant differences in reducing exacerbations and growth in height of the participants in the daily IFP or the episodic ISFP groups over a six-month period. There were no serious side effects from using the combination of salmeterol/fluticasone propionate in children with recurrent wheezing. Further studies are needed to evaluate the long-term efficacy of treatment with an intermittent inhaled long-acting $beta_2$-agonist combined with corticosteroids in asthma control.

## Acknowledgement

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