Linear Growth of Prepubertal Asthmatic Thai Children Receiving Long-term Inhaled Corticosteroids†

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Abstact

Background : Long-term inhaled corticosteroids are recommended in persistent asthma in children. The aim of this study was to determine the growth rate of asthmatic Thai children who received long-term inhaled corticosteroids.

Method : This controlled clinical trial was carried out on 145 prepubertal asthmatic Thai children, 81 in the study group (the group who received long-term inhaled corticosteroids) and 64 in the control group.

Results : The mean age of the patients when the study began was 5.9 years in the study group and 4.7 years in the control group. The average dose of inhaled corticosteroids used was 300 μg/day. The average duration overtime of inhaled corticosteroid usage was 2 years (9 months - 5 years).

The study showed that inhaled corticosteroids (300 μg/day for 9-60 months) have no significant effects on growth rate. From linear regression analysis, the factors that influenced the growth rate of asthmatic patients were the severity of the asthma and the age of the patients when nasal corticosteroids were started.

Insulin-like Growth Factor 1 (IGF 1) and Insulin-like Growth Factor Binding Protein 3 (IGFBP 3), were measured in 7 patients in the study group and 5 in the control group. All were normal, the height standard deviation score (Ht.SDS) was below average.

Conclusions : The average dose of inhaled corticosteroids (300 μg/day for 9 months) has no significant effects on the growth rate of prepubertal asthmatic Thai children.

Key word : Asthma, Height Standard Deviation Score, Inhaled Corticosteroids, Nasal Corticosteroids, Weight Standard Deviation Score

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Asthma is a common chronic disease in children. The incidence of asthma has increased all over the world. In Thailand, the incidence has increased from 2.39 per cent in 1975 to 4.29 per cent and 13 per cent in 1990 and 1998 respectively[1,2]. The pathophysiology and treatment of asthma have been widely studied. Asthma is a disease of conductive airway inflammation and anti-inflammatory drugs are helpful in its prevention. Corticosteroids are the most helpful anti-inflammatory drugs for the prevention of asthma. There is a high incidence of systemic side effects when used as systemic medication[3]. Because of the systemic side effects, inhaled corticosteroid therapy is prescribed instead of systemic corticosteroids.

Inhaled corticosteroid therapy is recommended in chronic asthma, even in mild persistent cases[4,5]. The side effects of inhaled corticosteroids are controversial[6-13]. Most of the studies have shown no side effects from short-term use of inhaled corticosteroids but some have shown side effects [6,7]. The side effects reported in long-term use of inhaled corticosteroids are Hypothalamic Pituitary Adrenal (HPA) axis and height suppression[8-10]. Some of the studies have shown no side effects with long-term use of inhaled corticosteroids[11-13]. There are few studies concerning the side effects of long-term use of nasal corticosteroids in children. One study showed growth suppression in children after one year of nasal beclometasone dipropionate (BDP) 168 μg/day[14]. There have been no studies in prepubertal asthmatic Thai children concerning growth rate after long-term use of inhaled or nasal corticosteroids.

The aim of this study was to determine the height rate of prepubertal asthmatic Thai children who received long-term inhaled corticosteroids.

MATERIAL AND METHOD

This controlled clinical trial was carried out on 145 Thai prepubertal asthmatic children who attended the Pediatric Allergy Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. All of them were seen by Pediatric allergists. They had no other systemic diseases. Demographic clinical data such as age, sex, family history, environmental factors, predisposing factors, time of diagnosis, severity of disease, frequency of attack, admission, medications and parental height were recorded. The severity of asthma and treatment followed the established guidelines[4,5].

The selected asthmatic children were divided into 2 groups by parents' decision after the doctor had explained the trial to them.

1. The study group: asthmatic children who had received continuous inhaled corticosteroids for at least 9 months. The patients were randomly prescribed metered inhaled beclomethasone or budesonide with a spacer device.

2. The control group: asthmatic children who did not receive inhaled or nasal corticosteroids. They should not receive systemic corticosteroids for an acute exacerbation for $\geq$ 2 weeks per year.

The patients were followed-up every 2-3 months. Height, weight and other medical information were recorded at every visit. Height was measured with a Harpenden stadiometer. Both height and weight were measured by the same nurse who was blind to the patient's status. The patients in the treatment group who stopped using inhaled corticosteroids before 9 months and patients in the control group who used inhaled or nasal corticosteroids during the study were excluded from the study. The patients in both groups did not reach puberty before the end of the study.

Height Standard Deviation Score (Ht.SDS) and Weight Standard Deviation Score (Wt.SDS) were calculated using the Tanner-White house program at each visit.

$$\text{Ht.SDS} = \frac{\text{Measured height - Predicted height}}{\text{Height standard deviation}}$$

$$\text{Wt.SDS} = \frac{\text{Measured weight - Predicted weight}}{\text{Weight standard deviation}}$$

IGF 1, IGFBP 3 and morning serum cortisol levels were measured in those with moderate persistent symptoms who received a dose of total topical (inhaled with or without nasal) corticosteroids $\geq$ 300 mg/day for more than 2 years and in an age-matched moderate persistent control. IGF 1 and IGFBP 3 were measured using immunoradiometric assay from Diagnostic System Laboratory. Normal value of IGF 1 and IGFBP 3 in Thai children have been shown in a previous report[15].

The Paired *t* test and one-way ANOVA were used in statistical analysis.

RESULTS

Eighty-one of 145 prepubertal asthmatic children included in this study were in the study

group (the group who received long-term inhaled corticosteroids with or without nasal corticosteroids) and 64 were in the control group (the group without inhaled or nasal corticosteroids). The mean age of the patients in the study group was significantly higher than in the control group (5.9 *vs* 4.7 years). Mean age when asthma started, Ht.SDS and Wt.SDS were not significantly different between both groups. There was no significant difference in skin prick test results or a family history of atopy in either group. In the study group, 6 per cent had mild persistent asthma and 94 per cent had moderate persistent asthma, while in the control group 12 per cent had mild persistent asthma and 88 per cent had moderate persistent asthma.

The average dose of inhaled and nasal corticosteroids used in study group was 300 (200-800) μg/day. Inhaled corticosteroids alone were used in 60 per cent of the cases in the study group while the rest used both inhaled and nasal corticosteroids. Fifty two per cent of the corticosteroids used in this study were beclometasone dipropionate (BDP) and 48 per cent was budesonide (BUD). The average duration of inhaled corticosteroid usage was 2 years (9 months - 5 years). The study showed that long-term use of inhaled corticosteroids can significantly reduce asthmatic symptoms, use of other antiasthmatic medications and admission rate ($p<0.01$). The growth rate of the children in both groups was not significantly different (5.8±0.4 cm/year in the treatment group *vs* 5.5±0.4 cm/year in the control group).

The severity of the asthma showed a positive correlation with the Ht.SDS but not Wt.SDS in both groups. A total dose of inhaled and nasal corticosteroids of more than 400 μg/day produced some depression of the Ht.SDS (Fig. 1) but this was not significant. The cumulative dosage of inhaled corticosteroids showed an inverse correlation with the Ht.SDS.

Inhaled corticosteroids therapy showed no significant effects on the Ht.SDS and Wt.SDS at any time but nasal corticosteroid therapy showed a significant reduction in the Ht.SDS in the study group 24 months after treatment (Fig. 2). From linear regression analysis, the factors that influenced the Ht.SDS of asthmatic children are the asthma severity and the age of the patients when nasal corticosteroids therapy was started (Table 1). No

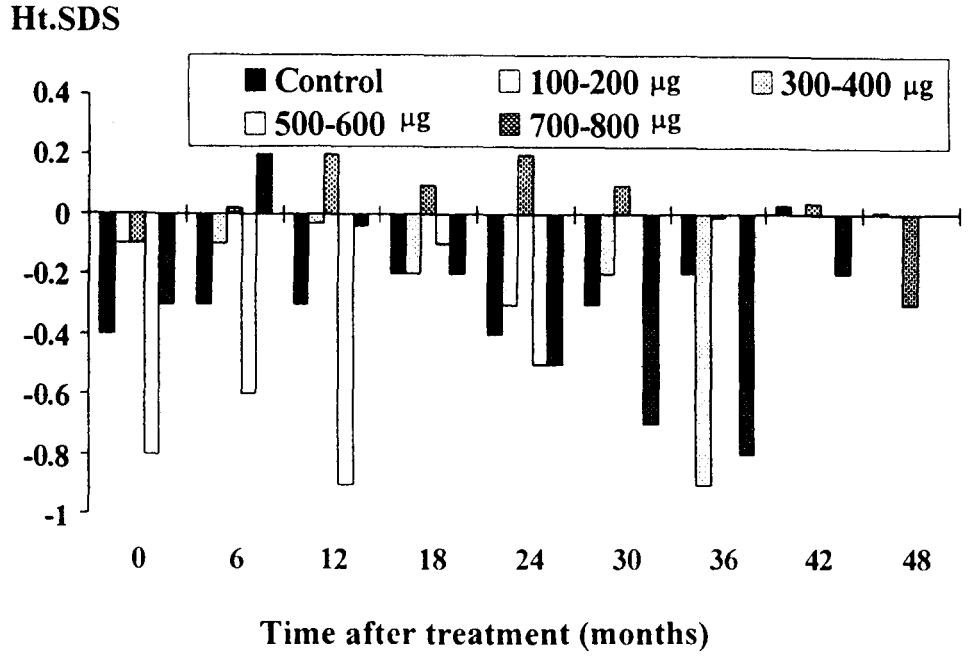

Fig. 1. Height standard deviation score (Ht.SDS) in asthmatic children at different times in controls and patients who received different doses of inhaled corticosteroids.

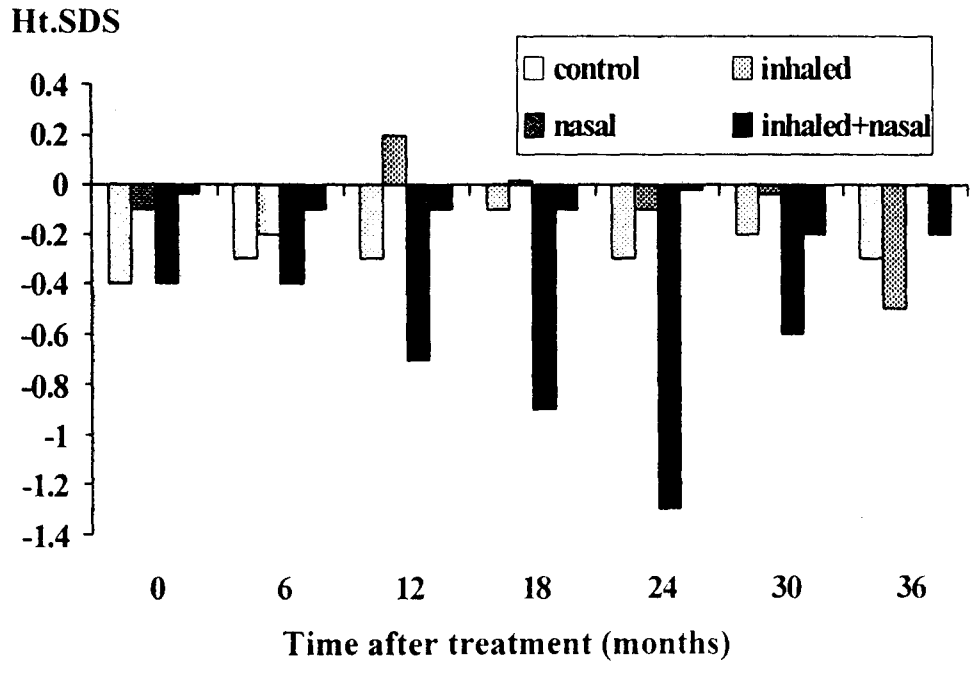

Fig. 2. Height standard deviation score (Ht.SDS) in asthmatic children at different times in control and patients who received inhaled and/or nasal corticosteroids.

Table 1. Factors affecting the height standard deviation score (Ht.SDS) in Thai asthmatic children.

Months after treatment	R square of factors influencing Ht.SDS			
	Age when nasal Corticosteroids started	P value	Asthma severity	P value
0	24.7	0.01	38.2	0.039
6	27.2	0.008		
12			34.7	0.003
18	48.5	0.002		
24	66.4	0.001		

local corticosteroid side effects such as candidiasis, dysphonia, cough, bronchospasm and contact allergy were found in this study.

IGF 1, IGFBP 3 and serum cortisol levels were measured in 7 patients with moderate persistent asthma in the study group and 5 in the control group. IGF 1 and IGFBP 3 were normal in all of them, while the Ht.SDS was below average (Fig. 3A and 3B). There was no significant difference in serum cortisol levels between the study and control groups. In this study, IGF 1 and IGFBP 3 levels showed no correlation with Ht.SDS.

Eighteen patients in the study and 11 in the control group are now 17 years old and all have achieved their expected adult height.

DISCUSSION

This study was performed to determine the growth rate of Thai asthmatic children who received long-term inhaled corticosteroid therapy. The study

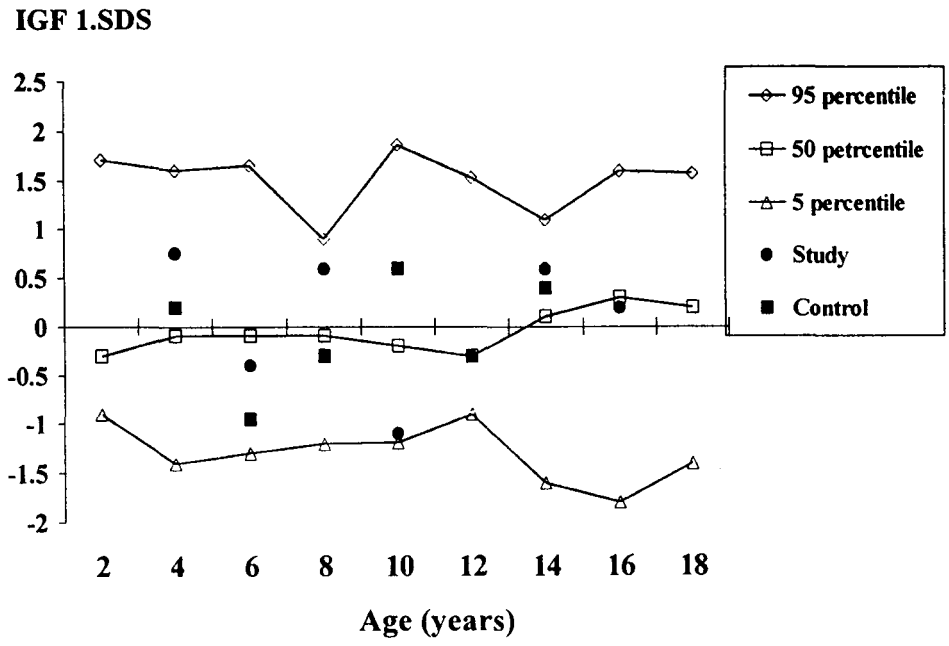

Fig. 3A. Insulin-like Growth Factor 1 standard deviation score (IGF 1.SDS) in the control and inhaled corticosteroid treatment groups.

was done in prepubertal children to avoid the effects of puberty on growth. Administration of inhaled or nasal corticosteroids in young children is still controversial because of fear of that these drugs suppress growth. Inhaled and nasal corticosteroids are the treatment of choice for inflammation in asthma and allergic rhinitis. In the treatment guidelines for asthma and allergic rhinitis, inhaled and nasal corticosteroids are not the first line of treatment in those less than 5 years of age with mild persistent symptoms[4,5,16]. Using these guidelines, every case with moderate and severe persistent asthma should receive inhaled corticosteroids[4,5]. In this study, most of the children had moderate persistent asthma and needed to receive inhaled corticosteroids therapy. However, the parents in the control group refused inhaled corticosteroid therapy despite explaining the benefit of therapy. In this study, patients who received inhaled corticosteroids therapy had significantly reduced symptom scores, antiasthmatic drug usage and admission rate.

This study shows that the severity of asthma has a positive correlation with Ht.SDS in both the study and control groups. Studies have shown that severe asthma affects the growth of asthmatic children and appropriate treatment improved both the severity of the asthma and the growth rate[17,18]. In this study, inhaled corticosteriods (BDP or BUD) > 400 μg/day can suppress the Ht.SDS but not significantly but the cumulative dosage of topical corticosteroids showed an inverse relationship with the Ht.SDS. Previous studies have shown that the suppression of HPA axis occurs only after long-term use of inhaled BUD or BDP ≥ 400 μg/day[8,9] but that suppression might occur using higher doses for a shorter time[6]. Most of the studies have shown dose-dependent suppression[9] but one showed suppression that was independent of dose[19]. In children, the use of inhaled BUD 200 μg/day for 3-5 years showed no effects on the HPA axis, growth and bone metabolism[20]. Inhaled fluticasone (FP) is available in Thailand now, but it is much more expensive than inhaled BUD or BDP. One study has shown that inhaled FP 200 μg/day affected the HPA axis, growth and bone metabolism when used ≥ 2 weeks[7].

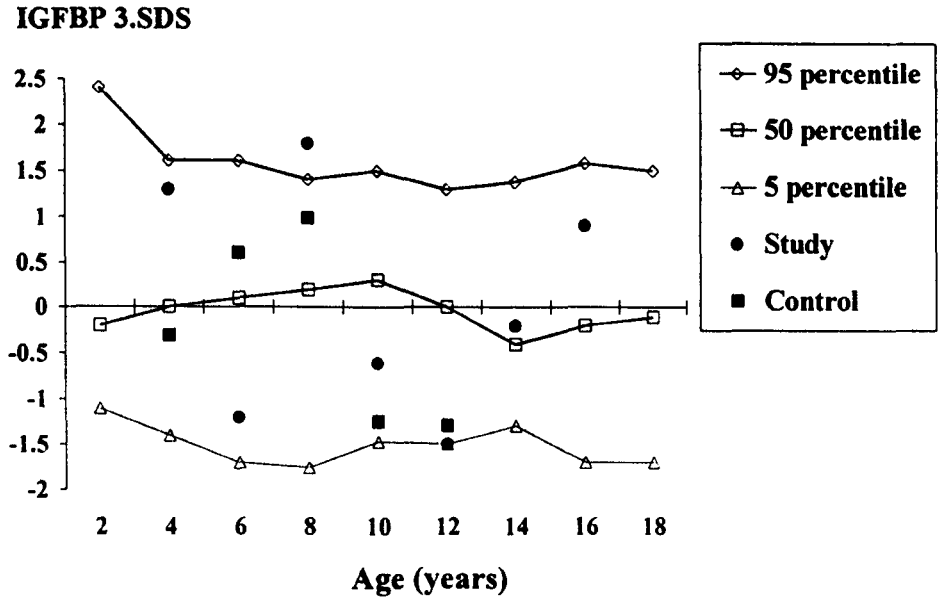

Fig. 3B. Insulin-like Growth Factor Binding Protein 3 standard deviation score (IGFBP 3.SDS) in the control and inhaled corticosteroid treatment groups.

Nasal corticosteroids, BUD or BDP, were allowed in addition to inhaled corticosteroids in the treatment group who had moderate persistent allergic rhinitis in this study. The pharmacokinetics of nasal corticosteroids may be different from inhaled corticosteroids but this is still not clear. This study shows that the age at which nasal corticosteroids were started has a significant effect on growth rate. If the patients received nasal corticosteroids before the age of 2, they had a higher chance of height suppression. Two studies have shown that nasal BUD $\leq$ 200 µg/day for more than 6 weeks[21] and one year[14] had an effect on growth in children but no significant effect in adults[22].

The present study shows that IGF 1, IGFBP 3 and serum cortisol levels have no correlation with Ht.SDS and long-term use of inhaled BUD and BDP at $\geq$ 300 µg/day but the number of cases was too small to make a firm conclusion. A previous study in prepubertal children with asthma who received inhaled 200-800 µg/day for 18 days showed no suppression of IGF 1 and IGFBP 3[23].

Thai children with mild and moderate persistent asthma can achieve their expected adult height if they receive appropriate management[17]. A 13-year follow-up study showed that asthmatic patients who received inhaled corticosteroids 400-600 µg/day reached their expected final height but had retardation of puberty[24]. In this study, the children in both the study and control groups have a trend to their expected adult height but the number of adolescent patients was too small to make a conclusion.

SUMMARY

This study showed that long-term use of inhaled corticosteroids with or without nasal corticosteroids (BUD or BDP) at 300 µg/day for 9 months had no significant effects on height and weight of prepubertal asthmatic Thai children. The severity of asthma and age of the patients when nasal corticosteroids were started showed significant effects on the height of asthmatic Thai children.

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ผลของยาสเตียรอยด์ชนิดสูดดมกับความสูงของเด็กไทยวัยก่อนหนุ่มสาวที่เป็นโรคหอบหืด†

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การใช้ยาพ่นคอร์ติโคสเตียรอยด์ระยะยาวในการรักษาโรคหืดเรื้อรังในเด็กซึ่งกำลังเจริญเติบโตนั้นยังเป็นที่วิจารณ์กันอยู่ว่าจะมีผลต่อการเจริญเติบโตเพียงใด ดังนั้นการศึกษานี้จึงศึกษาอัตราส่วนสูงในเด็กไทยที่เป็นโรคหอบหืด ช่วงอายุก่อนวัยรุ่นในกลุ่มที่ใช้ยาพ่นคอร์ติโคสเตียรอยด์ระยะยาวเทียบกับกลุ่มที่ไม่ได้รับยา

การศึกษาเป็นแบบ Controlled clinical trial ในเด็กไทยที่เป็นโรคหืดช่วงอายุก่อนวัยรุ่นจำนวน 145 คน โดยอยู่ในกลุ่มได้รับยา 81 คน อยู่ในกลุ่มไม่ได้รับยา 64 คน

ผลการศึกษาพบว่า อัตราส่วนสูงของผู้ป่วยเด็กในกลุ่มที่ได้รับยาพ่นคอร์ติโคสเตียรอยด์เฉลี่ย 300 μg/วัน ในระยะเวลาเฉลี่ย 2 ปี (9–60 เดือน) ไม่แตกต่างอย่างมีนัยสำคัญจากกลุ่มที่ไม่ได้พ่นยา และปัจจัยที่มีผลต่ออัตราส่วนสูงของเด็กที่เป็นโรคหอบหืดคือ ความรุนแรงของอาการโรคหืดและอายุที่เริ่มพ่นยาคอร์ติโคสเตียรอยด์ทางจมูกในกรณีที่ผู้ป่วยมีอาการทางจมูกร่วมด้วย

สรุป : ขนาดยาพ่นคอร์ติโคสเตียรอยด์เฉลี่ย 300 μg/วัน ในระยะเวลา 9 เดือนไม่มีผลต่ออัตราส่วนสูงของเด็กไทยที่เป็นโรคหืดช่วงอายุก่อนวัยรุ่น

คำสำคัญ : โรคหอบหืด, ยาพ่นคอร์ติโคสเตียรอยด์, อัตราส่วนสูง

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