Relationship between inhaled steroids and anthropometric status of pediatric patients with chronic asthma

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ABSTRACT

Background: Asthma is a chronic inflammatory respiratory disease characterized by breathlessness, wheezing, and coughing symptoms. Asthma management aims to control the frequency of asthma exacerbations and ensure optimal growth and development in children. Inhaled steroids are anti-inflammatory medications that inhibit the synthesis of pro-inflammatory cytokines such as IL-4, IL-9, IL-13, and IL-17, which play a role in the pathogenesis of asthma. However, using inhaled steroids at high doses and for a long duration can have side effects on children's height. This research aims to examine the relationship between the use of inhaled steroids and the growth in height of children with asthma.
Methods: simple linear regression analysis and multiple linear regression analysis.
Results: the analysis indicate a correlation between daily dose and height increment in children aged 5-10 years ($p = 0.005 < 0.05$), but no significant correlation was found in children aged 10-18 years ($p = 0.722 > 0.05$). The analysis of total duration shows a correlation with height increment in both age groups (5-10 years, $p = 0.035 < 0.05$; 10-18 years, $p = 0.001 < 0.05$). The analysis also reveals a correlation between the simultaneous total duration and total dose with height increment in both age groups (5-10 years, $p = 0.005 < 0.05$; 10-18 years, $p = 0.008 < 0.05$).
Conclusion: this study found a correlation between daily dose and height in both age groups, a correlation between total duration and height in the 5-10-year-old age group, and a correlation between simultaneous total duration and total dose with height in both age groups.

INTRODUCTION

Asthma is a chronic inflammatory respiratory disease characterized by breathlessness, wheezing, and coughing symptoms. The prevalence of childhood asthma in Indonesia based on the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire data from 2008 to 2017 indicates that it affects approximately 4-11% of children in the age group of 6-7 years and 4-11% in the age group of 13-14 years. Asthma triggers include allergens such as air pollution, house dust mites, respiratory infections, and medications.[1,2]

Management of asthma with inhaled steroids aims to control the frequency of asthma exacerbations. Inhaled steroids have anti-inflammatory effects and work by inhibiting the synthesis of pro-inflammatory cytokines such as IL-4, IL-9, and IL-13, which can stimulate the release of IgE by B cells, triggering mast cell degranulation and the release of histamine and leukotrienes, leading to bronchoconstriction. Some inhaled steroids include budesonide, fluticasone propionate, and beclomethasone dipropionate. The effectiveness of therapy using inhaled steroids is determined by the type of inhaler device and proper inhalation technique by the patient.[3,4]

Using inhaled steroids as asthma controller medication can cause local and systemic side effects. Local side effects such as candidiasis are caused by the deposition of corticosteroids in the oral cavity and esophagus. On a systemic level, corticosteroids can hinder height growth in children by disrupting growth hormone release, inhibiting IGF-1 activity and osteoblast function, and suppressing collagen synthesis. The inhibition of bone formation due to corticosteroids is based on the hindrance of calcium absorption in the intestines and increased urinary excretion of calcium. The inhibition of height growth as one of the side effects of inhaled steroids is influenced by the dosage and duration of medication administration.[5,6] Therefore, this study aims to examine the relationship between the dosage and duration of inhaled steroid administration and the side effects on children's height growth

MATERIALS AND METHODS

Study Design

This study adopts an analytical observational design with a cross-sectional study design to examine the relationship

between the use of inhaled steroids and the side effects on the height growth of children with chronic asthma at Saiful Anwar Hospital in Malang.

Study Sample

The study sample consists of pediatric patients aged 10-18 years diagnosed with chronic asthm currently receive inhaled steroid therapy at Saiful Anwar Hospital in Malang. The consecutive sampling technique will be used for sample selection. The inclusion criteria include pediatric asthma patients aged 10-18 years who are undergoing inhaled steroid therapy and are not concurrently receiving oral steroids.

Research Instrument

The research instrument used in this study is the medical records from Saiful Anwar Hospital in Malang, which serve as the data source for the dosage and duration of inhaled steroids and the height of the children.

Data analysis in this study will involve correlation analysis to determine the relationship between two variables. The choice of correlation test will depend on the distribution of the data. If the data distribution is abnormal, the Spearman's rank correlation test will be used. On the other hand, if the data distribution is normal, the Pearson correlation test will be employed.

The data processing in this research uses the method of simple linear regression to examine the relationship between daily dosage and total duration with children's height, and multiple linear regression to examine the relationship between total duration and simultaneous total dosage with children's height.

RESULTS

The sample used in this study consisted of 27 participants who met the inclusion criteria: asthma patients currently using inhaled steroids and not receiving oral steroid therapy.

Based on Table 1 below, the research subjects were found to have a nearly balanced distribution between the two genders, with 14 males and 13 females. Most subjects were aged 5-10 years, with 18 individuals falling within this age range. Additionally, most subjects had a moderate persistent asthma severity level, comprising 15 individuals.

Based on Table 2 above, the most commonly used type of inhaled steroid is fluticasone propionate, accounting for 17 samples (62.96%). The daily dosage for the age groups of 5-10 years and 10-18 years

Table 1. Subject Characteristic

	Frequency
Sex	
Men	14
Woman	13
Age (years)	
5-10	18
10-18	9
Severity level of asthma	
Intermitten asthma	5
Mild persistent asthma	4
Moderate persistent asthma	15
Severe persistent asthma	3

Table 2. Characteristics of inhaled steroids

	Frequency
Types of inhaled steroids	
Budesonide	5
Fluticasone propionate	17
Budesonide–Fluticasone propionate	5
A daily dose of inhaled steroids	
5-10 years old (mcg/day)	
<200	6
200-400	10
>400	2
10-18 years old	
<200	1
200-400	5
>400	3
Duration steroids treatment	
<6 month	8
6-12 month	7
>12 month	12

Table 3. Descriptive statistics group of 5-10 years

	Min.	Max.	Mean	SD
Daily dose	50.0	712.07	275.09	194.7
Total dose	3200	872450	137791.1	221600.5
Total of duration	1	812	269.70	257.2
Difference TB	.50	85.00	11.488	19.0

Table 4. Descriptive statistics group of 10-18 years

	Min	Max	Mean	SD
Daily dose	50.00	640.00	367.117	178.74
Totaldose	4900.00	464400.00	188061.	155013.7
Total duration	98.00	930.00	502.222	325.63
Difference TB	1.00	17.70	7.6111	5.926

Table 5. Relationship between daily dosage and height of children in the age group of 5-10 years

	R	Sig.
Daily dose	.632	.005

Table 6. Relationship between daily dosage and height of children in the age group of 10-18 years

	R	Sig.
Daily dose	.139	.722

Table 7. Relationship between total duration and height of children in the age group of 5-10 years

	R	Sig.
Total of duration	.499	.035

Table 8. Relationship between total duration and height of children in the age group of 10-18 years

	R	Sig.
Total of duration	.892	.001

Table 9. Relationship between total dosage and total duration with height of children aged 5-10 years

	t	Sig.
Total of duration	2.479	.026
Total dose	2.795	.014
	R	Sig.
Regression	.712	.005

Table 10. Relationship between total dosage and total duration with height of children aged 10-18 years

	t	Sig.
Total of duration	.161	.877
Total dose	2.045	.087
	R	Sig.
Regression	.892	.008b

mostly falls within the range of 200-400 mcg/day, with 10 samples (37.04%) and 5 samples (18.52%), respectively. A total of 12 samples (44.44%) used inhaled steroids for more than 12 months.

Based on Table 3, for the 18 samples of pediatric asthma patients in the age group of 5-10 years, the mean for the variable of daily dosage is 275.10, and the standard deviation is 194.71. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

For the variable of total dosage, the mean is 137791.11, and the standard deviation is 221600.56. This indicates that the data is heterogeneous because the standard deviation is higher than the mean.

For the variable of total duration, the mean is 269.70, and the standard deviation is 257.24. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

For the variable of height difference, the mean is 11.49, and the standard deviation is 19.09. This indicates that the data is heterogeneous because the standard deviation is larger than the mean.

Based on Table 4, for the samples of pediatric asthma patients in the age group of 10-18 years, the mean for the variable of daily dosage is 367.12, and the standard deviation is 178.74. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

For the variable of total duration, the mean is 188061.11, and the standard deviation is 155013.76. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

For the variable of total duration, the mean is 502.22, and the standard deviation is 325.63. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

For the variable of height difference, the mean is 7.61, and the standard deviation is 5.93. This indicates that the data is homogeneous because the standard deviation is smaller than the mean.

Relationship between inhaled steroids and height

Analysis of the relationship between daily dosage (mcg/day) of inhaled steroids and the increase in height of children resulted in a p-value (sig) of $0.005 < 0.05$ and a t-value of $3.262 > 2.131$. Therefore, it can be concluded that there is a significant relationship between daily dosage of inhaled steroids and the inhibition of height increase in children in the age group of 5-10 years. The R-value of 0.632 indicates a strong relationship between the independent and dependent variables.

Analysis of the relationship between daily dosage (mcg/day) of inhaled steroids and the increase in height of children resulted in a p-value (sig) of $0.722 > 0.05$ and a t-value of $0.371 < 2.447$. Therefore, it can be concluded that there is no significant relationship between daily dosage of inhaled steroids and the inhibition of height increase in children in the age group of 10-18 years.

Analysis of the relationship between total duration of inhaled steroid usage (in days) and the increase in height of children resulted in a p-value (sig) of $0.035 < 0.05$ and a t-value of $2.305 > 2.131$. Therefore, it can be concluded that there is a significant relationship between the total duration of inhaled steroid usage and the inhibition of height increase in children in the age group of 5-10 years. The R-value of 0.499 indicates a weak relationship between the independent and dependent variables.

Analysis of the relationship between total duration of inhaled steroid usage (in days) and the increase in height of children resulted in a p-value (sig) of $0.001 < 0.05$ and a t-value of $5.215 > 2.447$. Therefore, it can be concluded that there is a significant relationship between the total duration of inhaled steroid usage and the inhibition of height increase in children in the age group of 10-18 years. The R-value of 0.892 indicates a strong relationship between the independent and dependent variables.

Analysis of the relationship between total duration and total dosage with the increase in height of children resulted in a p-value (sig) for total dosage of $0.014 < 0.05$ and a p-value (sig) for total duration of $0.026 < 0.05$. Therefore, it can be concluded that there is a significant relationship between each independent

variable, total duration, and total dosage, with the inhibition of height increase in children in the age group of 5-10 years.

F-value of 7.694 > 3.63 and the p-value (sig) of 0.005 < 0.05 indicate a simultaneous relationship between the two independent variables, total duration and total dosage, with the inhibition of height increase in children aged 5-10 years.

The analysis of the relationship between total duration and total dosage with the increase in height of children resulted in a p-value (sig) for total dosage of 0.877 > 0.05 and a p-value (sig) for total duration of 0.087 > 0.05. Therefore, it can be concluded that there is no significant relationship between each independent variable, total duration, and total dosage, with the inhibition of height increase in children in the age group of 10-18 years.

F-value of 11.718 > 4.74 and the p-value (sig) of 0.008 < 0.05 indicate that there is a significant simultaneous relationship between the two independent variables, total duration and total dosage, with the dependent variable, which is the inhibition of height increase in children in the age group of 10-18 years.

DISCUSSION

This study observed the relationship between daily dosage, total duration, and total dosage of inhaled steroids with the anthropometric status of height in pediatric asthma patients. Inhaled steroids act as anti-inflammatory agents and reduce airway hyperresponsiveness in asthma patients. However, long-term and high-dose inhaled steroids can lead to side effects. These side effects include disturbances in the HPA axis, which can affect the pulsatile secretion of growth hormones, the bioactivity of IGF-1 as a secondary messenger, osteoblast activity, collagen synthesis, adrenal hormone production, as well as the absorption of calcium in the intestines and increased calcium excretion through urine, all of which can impact height growth.[7,8]

Analysis of the study revealed a strong correlation (r = 0.632, p = 0.005 < 0.05) between daily dosage (average dosage of 367.12 µg/day) and the anthropometric status of height in children aged 5-10 years. However, no significant correlation was found in the age group of 10-18 years

(p = 0.722 > 0.05). This is consistent with the study by Allen et al. (2015), which concluded that the dose-dependent side effects of inhaled steroids were more significant in pre-pubertal children than pubertal children. The magnitude of the growth hormone effect during the pre-pubertal phase is one of the factors contributing to the significant impact of inhaled steroids on height growth in this age group. The relationship between daily dosage of inhaled steroids and the inhibition of height growth was also observed in the study, where beclomethasone at a medium dose (100-200 µg/day) caused a more significant inhibition of height growth compared to a low dose (50-100 µg/day).[3] In contrast to the results of a retrospective observational study on a sample of 284 pre-pubertal children, which showed no significant difference between medium and low doses of inhaled steroid fluticasone propionate in terms of the side effect of inhibiting height growth in children.[6,7]

Analysis of the relationship between total duration and total dosage of inhaled steroids with the anthropometric status of height revealed a weak correlation between these variables in the age group of 5-10 years (r = 0.499, p = 0.35 < 0.05) and a strong correlation in the age group of 10-18 years (r = 0.892, p = 0.001 < 0.05).These findings are corelated by a systematic review involving 11 trials with 3,332 participants. The review observed a significant inhibition of height growth based on initial height measurements in participants who received inhaled steroids for more than 6 months.[3,7] The long-term effects of inhaled steroids on height were also observed in The Childhood Asthma Management Program (CAMP, 2000) study, which examined children aged 5-12 years with mild-to-moderate asthma. After 4.3 years of treatment with inhaled steroids, specifically budesonide at a dosage of 400 µg/day, the average height increment was 1.1 cm lower compared to the placebo group.[8,9]

A study in 2000 on 142 pediatric asthma patients treated with budesonide at an average daily dosage of 412 µg/day and an average duration of therapy of 9.2 years showed that the patients achieved normal adult height compared to the

control group.[4,10] Therefore, it can be concluded that the significant effect of inhaled steroids on height occurs in the first year of therapy, but children's height will catch up and reach their normal adult height.[11,12]

A study 2010 on prepubertal patients with moderate-to-severe persistent asthma who were treated with beclomethasone at an average daily dosage of 351.8 µg/day and a therapy duration of 5.2 years concluded that the daily dosage and therapy duration did not affect children's height according to age.[13,14] This finding contradicts the results of studies that show a relationship between total duration and the side effects of inhaled steroids on children's height.

Analysis of the simultaneous relationship between dosage and duration of inhaled steroid use as independent variables and the anthropometric status of height as the dependent variable showed a simultaneous relationship between the two independent variables and the dependent variable in both age groups (p-value for the age group 5-10 years = 0.005 > 0.05 and F-value for the age group 10-18 years = 0.008 > 0.05).

Limitations of this study mainly stem from the small sample size and as the researchers had no control over the data's validity. Out of 88 pediatric asthma patients aged 0-18 years at Saiful Anwar Hospital in Malang, only 27 samples met the inclusion criteria. The most common reason for sample exclusion was incomplete data on dosage and children's height in the medical records. Additionally, confounding variables such as patient compliance with inhaled steroid use and the severity of asthma, which directly affects the anthropometric status of height, were not considered. The study also lacks consideration of the influence of the type of inhaler device on the relationship between inhaled steroids and height, as different devices may have varying potential for steroid molecule delivery. The use of secondary data from medical records is also

CONCLUSION

Daily dosage of inhaled steroids is associated with the anthropometric status of height in pediatric asthma patients in the 5-10-year age group, but there is no

association in the 10-18-year age group. Total duration of steroid inhalation is associated with the anthropometric height status in pediatric asthma patients in both the 5-10-year and 10-18-year age groups. There is a relationship between the two variables, total duration and total dosage, and the anthropometric status of height in pediatric asthma patients in the 5-10-year and 10-18-year age groups. Further research is needed to investigate the impact of asthma severity and the type of device used as confounding variables. Objective measurements of height should be implemented to reduce bias in patient data.

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CONFLICTS OF INTEREST

The author declared that there is no conflict of interest.

AUTHOR CONTRIBUTION

All authors contributed equally in preparing and writing this manuscript.

ETHICAL APPROVAL

This research has been approved by the Ethics Commission of Saiful Anwar Hospital in Malang.

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