Research Article

The effect of alternate-day corticosteroids on linear growth in childhood nephrotic syndrome

R.S. Thalgahagoda[1], A.H.H.M. Jayaweera[1], Y.A. Illangasekera[2], A.S. Abeyagunawardena[1]

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Correspondence to:
Prof. A.S. Abeyagunawardena, Srilanka

Author's Affiliation:
1- Department of Paediatrics, Faculty of Medicine, University of Peradeniya, Sri Lanka
2- Department of Pharmacology, Faculty of medicine, University of Peradeniya, Sri Lanka

Abstract

Corticosteroids remain the mainstay treatment of childhood nephrotic syndrome (NS). Its deleterious effects on linear growth are well documented. However literature reveals that alternate day dosing has minimal effects on growth contrary to our observations. This study was carried out to ascertain the effects of alternate-day corticosteroids on linear growth in a stable population of patients with steroid dependent nephrotic syndrome (SDNS).

Materials and methods

The growth velocity of 40 patients (age 3.6-14.5yrs) with SDNS on alternate-day prednisolone was compared with that of an age and sex matched control sample comprising 40 patients with NS who were off steroids. Both populations were followed-up for one year. Height velocity was calculated from the respective heights at the onset and conclusion of the study, and compared using the Mann-Whitney U test.

Results

The average alternate-day prednisolone dose was 0.51mg/kg. The height velocity was 3.9 cm/year (SD 1.17) in the prednisolone treated group and 6.45cm/year (SD 1.44) in the control group. The difference was statistically highly significant ($U=134$, $z= -6.4$, $p<0.001$). The dose of prednisolone did not have a significant bearing on linear growth, with those on an average dose equal to or less than 0.5mg/kg being equally affected as those on a dose more than 0.5mg/kg.

Conclusion

The results of this study indicate that alternate day dosing of corticosteroids has deleterious effects linear growth, contrary to what has been reported in the literature. These deleterious effects are evident even with lower doses. We postulate that the low dietary protein content of the studied population could be the reason for these findings. The high protein diet in western populations may explain the difference in observations between our population and studies from the developed world.

Keywords: childhood nephrotic syndrome, steroid-dependent, linear growth, corticosteroids, IGF1, low protein diet

Introduction

Childhood nephrotic syndrome is characterized by massive proteinuria, hypoalbuminaemia and oedema. In the majority of patients the disease follows a relapsing and remitting course[1]. Corticosteroids remain the mainstay of treatment. For the first episode, steroids are given at a daily dose for four to six weeks followed by alternate day dosing for a further four to six weeks[2]. Relapses are treated with daily corticosteroids until remission is attained followed by alternate-day dosing which is tapered over a variable period of time. A proportion of patients remain steroid dependent and require continuation of alternate-day steroids for prolonged periods, usually with the addition of steroid sparing agents. Sepsis, thrombosis, malnutrition, dyslipidemia and hypovolemia are risks that are associated with relapses, while adverse effects such as hypertension, diabetes and behavioural disorders have been observed with high doses of steroids[3,4,5].

A main cause of linear growth retardation in nephrotic patients in the past when steroids were not prescribed was protein malnutrition due to poor appetite, loss due to proteinuria and malabsorption due to gastrointestinal tract oedema. However, in the present context corticosteroids are considered to be the major cause[6].The deleterious effects of corticosteroids on linear growth in children are well documented. Corticosteroids are thought to inhibit growth by multiple mechanisms including impaired release of growth hormone and decreased activity of insulin-like growth factor-1(IGF-1) on growing bones[7,8,9]. These effects are mainly seen with long-term and daily dosing regimens[10-15] and published data indicate that alternate-day dosing has minimal effects on growth[16]. This is contrary to observations made in our patient population, where growth failure is evident even in those patients on alternate-day steroids.

This difference in observation could be due to the dietary differences among our population of patients and patients from the developed world. The high protein content in western diets,

through its positive effects on IGF-1[17], may be masking the deleterious effects of corticosteroids on linear growth. It is possible that linear growth is affected in our population of patients, even with alternate day steroids, due to the paucity of dietary protein content.

Linear growth is an important aspect of childhood development. Growth impairment in childhood leads to social stigma as well as anxiety and emotional ill health. Optimizing growth is therefore of great importance. Identification that alternate day steroids affect linear growth could lead to a change in practice with earlier institution of steroid sparing agents in order to prevent growth retardation.

This study was undertaken to ascertain the effects of alternate-day corticosteroids on linear growth in a stable population of patients with steroid dependent nephrotic syndrome (SDNS).

Method

This was a single center observational study conducted from January 2012 to June 2013. All procedures were in accordance with the ethical standards of the Scientific and Ethics Committee, Faculty of Medicine of the University of Peradeniya, and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants.

Study population: The growth velocity of 40 patients with SDNS who were on alternate-day prednisolone was compared with that of an age and sex matched control sample comprising patients with NS who were off steroids and with that of an age and sex matched normal population. This normal population was a hypothetical population which was obtained from the Centers for Disease Control (CDC) growth charts which was age and sex matched to the study population[18]. The recruited subjects were followed up for a period of one year. The height velocity was calculated from the respective heights at the onset and conclusion of the study and the height velocities of the three groups were compared. A minimum sample size of 31 subjects

per study arm was calculated based on a power of 90% to detect a 20% reduction in height velocity at a 95% confidence interval[19]. The respective growth velocities of the study and control populations were compared using the Mann-Whitney U test.

Patients for both the study population and the control population were recruited from patients attending the paediatric nephrology clinic at Teaching Hospital, Peradeniya. The inclusion criteria for the study group were as follows;

- All patients with steroid-dependent nephrotic syndrome between ages one and sixteen who were on alternate day prednisolone and who had not had a relapse and therefore had not been on daily corticosteroids in the three months preceding the study.

The exclusion criteria for the study group were as follows;

- Patients with secondary nephrotic syndrome.
- Patients below one year and above sixteen years of age.
- Patients with other concomitant conditions that can affect growth.
- Patients with impaired renal function.

The control group consisted of patients with idiopathic steroid sensitive nephrotic syndrome who were off corticosteroids and who had not received corticosteroids in the three months preceding inclusion in the study.

Patients on steroid sparing alternative medication were also included and these were recorded in the respective groups.

All patients in the study and control groups who relapsed during the study period and were thus commenced on daily corticosteroids were excluded from the study.

Patients enrolled in the study had their heights measured with the help of a stadiometer using the standard five point technique proposed by the World Health Organisation[20] by specially trained

personnel. Height was measured in centimeters at enrolment and one year later. The increment in height over the one year period was obtained in cm/per year and this value was considered as the height velocity. The dose of alternate day prednisolone at enrolment and all subsequent dose changes were documented and the average prednisolone dose was obtained. The average dose was correlated with the height velocity.

Results

All subjects belonging to both the study and control groups completed the study giving a population of 40 for each arm. The average alternate-day prednisolone dose was 0.51mg/kg. The basic characteristics of the study groups are shown in Table 1.

Table 1: Basic characteristics of study groups

	Study Group	**Control Group**	**Normal Population**	
n	40	40	40	
Age years (mean ± SD)	7.9 ± 2.9	7.8 ± 2.9	7.9 ± 2.9	p>0.05*
Gender female *n*(%)	13 (32.5)	13 (32.5)	13 (32.5)	
Drug therapy				
Prednisolone + Levamisole *n*(%)	28 (70)	-		
Prednisolone + Cyclosporine A *n*(%)	12 (30)	-		
Levamisole *n*(%)	-	36 (90)		
Cyclosporine *n*(%)	-	04 (10)		

p*- students t-test

The mean ages of the participants were 7.9 ± SD2.9 years and 7.8 ± SD2.9 years for the prednisolone and control groups respectively (p>0.05). There was also no significant difference in the initial average height between cases (117.8 ± SD16.4 cm) and controls (120.7 ± SD16.0 cm). The mean age of subjects from the normal population was 7.9 ± SD2.9 years.

In the study population 28/40 patients were on prednisolone and levamisole while 12/40 patients were on prednisolone and cyclosporine A. In the control group 36/40 patients were on levamisole alone while 4/40 patients were on cyclosporine A alone. The comparison of median height velocities across the study, control and normal population groups are displayed in figure

1. The median height velocity of the study group was 3.45 cm/year which was significantly lower than the height velocity of 6.15 cm/year calculated for the control group (U=134, z= -6.4, p<0.001). The height velocity in the control population tended to be higher than the normal population (mean 5.55 cm/year), though the difference was not statistically significant. (U=604, z= -1.88, p=0.06). Conceivably, the height velocity of the prednisolone group was also significantly lower than that in the normal population (p<0.001).

The effect of the prednisolone dosage on height velocity is displayed in figure 2. The dose of prednisolone did not have a significant bearing on linear growth, with those on an average dose equal to or less than 0.5mg/kg (3.3cm/year, N=15) being equally affected as those on a dose more than 0.5mg/kg (4cm/year, N=25). (U=152, z= -.994, p0.332)

Patients above 10 years of age tended to be more affected than those below. No difference was observed between the growth velocities of males and females in either of the groups.

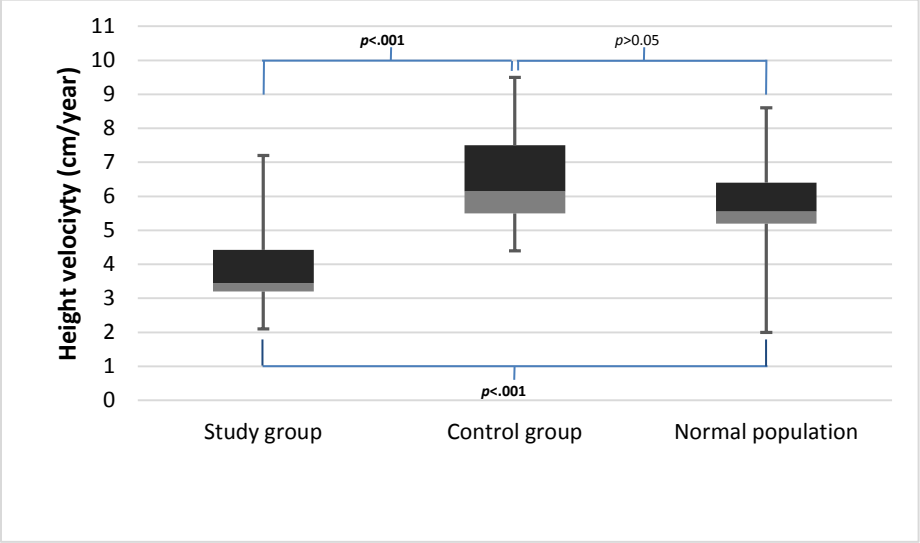

Figure 1. Comparison of median height velocities between groups

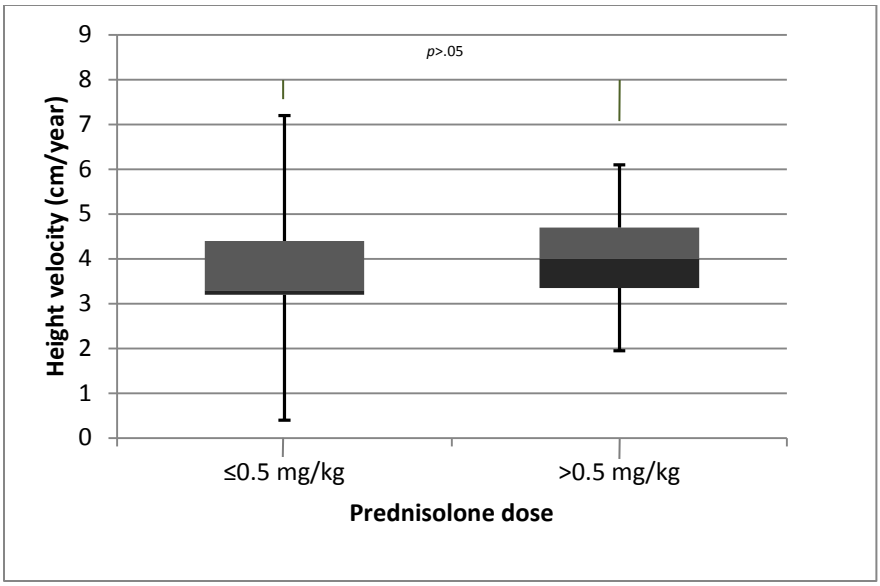

Figure 2. Effect of prednisolone dose on median height velocity

Discussion

Retardation of growth in children and adolescents can have major social and psychological implications. Therefore preservation of growth is an important aspect of management even in conditions that necessitate treatment with long term corticosteroids.

The results of this study indicate that alternate day corticosteroids affect linear growth. We also found that these deleterious effects are evident even at lower doses (less than 0.5mg per kg body weight). These findings confirm our observation that growth does seem to be affected even in patients on low dose alternate day corticosteroids. The control population also comprised patients with NS. Therefore no bias could be attributed to the underlying disease.

Some studies have observed linear growth retardation secondary to prolonged steroid treatment in children with nephrotic syndrome[12,13,14]. However, results contrary to these and the present study are reported widely in the literature. Simmonds *et al*[15] in their study performed on a similar population of patients at Great Ormond Street Hospital in the United Kingdom found that low to

moderate doses of prednisolone had no effect on linear growth. This was true even at doses up to 0.75mg/kg, though doses above 0.75mg/kg had a small but significant deleterious effect on growth velocity. Polito *et al*[16]reported similar results with alternate day corticosteroids in pre-pubertal children with nephrotic syndrome.

The reason for this difference in observation is unclear. Fontana *et al*[17] demonstrated a reduction in IGF1 concentrations in patients with a low protein intake. The population studied is from the developing world where dietary protein content is known to be low due to economic and cultural reasons. This low protein content could have negative effects on IGF1 levels. The high protein diet in western populations may be the reason why the negative effects of steroids on growth are not seen. This could explain the difference in observations between our population and studies from the developed world.

Another interesting finding in our study is the high growth rate observed in the control population. This rate tended to be higher than that in the normal population as well, though the difference did not reach statistical significance. This could be explained by the phenomenon of catch up growth where a rapid growth rate is observed when corticosteroids are withdrawn. Foote *et al*[21] reported normal ultimate height attainment due to catch up growth following withdrawal from steroids in patients with nephrotic syndrome. This phenomenon was also seen in the study by Simmonds *et al*.

A weakness of this study is that we have not considered the effects of puberty on linear growth in our population, though we observed that growth tended to be affected more in those over 10 years of age. Long term corticosteroids have been shown to delay puberty[11,22] and one could argue that a delay in puberty could have contributed to the low linear growth velocity in our study population. However our study population consisted mainly of pre-pubertal children with a

mean age of 7.9 ± 2.9 years. Only 7 of the 40 subjects in the study group were over the age of 10 years. We therefore feel that the effects on linear growth in the study population could not be attributable to delayed puberty alone. We could not study the effect of steroids on the pubertal age group separately as the small number of patients precluded drawing any statistically significant conclusions.

The findings of this study indicate that linear growth is affected even at relatively lower doses of steroids. The implications of this finding are that the need for steroid sparing agents becomes more important in our population of patients. The use of less toxic steroid sparing agents like levamisole early in the course of the disease could help to taper and withdraw steroids completely, thereby improving growth.

In summary we have shown that alternate day corticosteroids affect linear growth in a stable population of patients from the developing world with steroid sensitive nephrotic syndrome. This effect is seen even at doses of prednisolone less than 0.5mg/kg. The low protein diet in our population, through its negative effects on IGF1, could be the reason for the difference in observations in our study and those from the developed world.

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