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Efficacy and safety of growth hormone treatment for children born small for gestational age

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Recombinant growth hormone (GH) is an effective treatment for short children who are born small for gestational age (SGA). Short children born SGA who fail to demonstrate catch-up growth by 2–4 years of age are candidates for GH treatment initiated to achieve catch-up growth to a normal height in early childhood, maintain a normal height gain throughout childhood, and achieve an adult height within the normal target range. GH treatment at a dose of 35–70 μg/kg/day should be considered for those with very marked growth retardation, as these patients require rapid catch-up growth. Factors associated with response to GH treatment during the initial 2–3 years of therapy include age and height standard deviation scores at the start of therapy, midparental height, and GH dose. Adverse events due to GH treatment are no more common in the SGA population than in other conditions treated with GH. Early surveillance in growth clinics is strongly recommended for children born SGA who have not caught up. Although high dose of up to 0.067 mg/kg/day are relatively safe for short children with growth failure, clinicians need to remain aware of long-term mortality and morbidity after GH treatment.

Key words: Infant, Small for gestational age infant, Growth hormone, Treatment outcome, Safety

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Introduction

Depending on the definition used, between 3% and 10% of all live neonates worldwide are born small for gestational age (SGA). SGA is associated with an increased risk of insulin resistance, obesity, cardiovascular disease, and type 2 diabetes mellitus. Most children born SGA have normal adrenarche and pubarche and normal pubertal development timing. Onset of puberty occurs at normal age, but relatively early within the normal range and, in some children, unexpectedly early for their short stature[1]. About 80%–85% of children born SGA experience rapid catch-up growth during the first 12 months of life, while 10%–15% do not experience catch-up growth[2-4]. The use of GH in short children born SGA has been explored for nearly 40 years[5-7]. This review will discuss the effects and safety of GH treatment in short children born SGA (Table 1).

Definition of SGA

In Korea, 721,074 children were born in 1995, followed by a shrinking birth rate trend; the number of births fell to 438,062 in 2005, and slightly increased to 496,710 in 2007. The percentage of children with a birth weight of less than 2.4 kg was 3.0% in 1995, and 4.6% in 2007. The percentage of children with a birth weight less than 1.5 kg was 0.16% in 1995, and 0.46% in 2007. According to these data from Korea's National Statistical Office, the number of children with low birth weight has been clearly increasing[8]. Various

definitions have been used to define low birth weight, depending on whether a percentile or standard deviation (SD) below the mean is used. The World Health Organization has defined it as a birth weight of less than 2,500 g[9].

Birth weight, length and/or head circumference below the 10th percentile for gestational age have been used by neonatologists to define SGA[10,11]. The most common definition of SGA is a birth weight and/or length of less than −2 SD from the mean in relation to gestational age for the same sex. This cutoff point corresponds to the 2.3 percentile for gestational age. Intrauterine growth retardation, a term often used synonymously with SGA, suggests an underlying pathophysiological process that prevents the fetus from achieving its inherent potential growth, or a proven growth restriction before birth.

There are multiple causes of SGA, and they include a variety of fetal, maternal, placental and demographic factors[12-14]. No cause has been identified, however for 40% of infants born SGA, and this figure increases to 60%–70% in premature infants born SGA[15].

Catch-up growth

Approximately 80%–85% of children born SGA experience a rapid catch-up growth period during the first 12 months of life, while 10%–15% lack this period of catch-up growth[2-4]. Accelerated growth begins 2 weeks to 3 months after birth. Average weight and length increase from the 10th to the 25th percentile at 6 months. Most children born premature and SGA have a slower and more prolonged catch-up growth period than term SGA children , and it can take 4 or more years for the premature children to fully catch up[16].

Birth length is the most important predictor for catch-up growth but no associations with gestational age, multiple births, and sex [2,3,17].

Among children who are born SGA without catch-up growth by 2 years of age, the relative risk of short stature at 18 years of age is 5.2 for those born lighter than normal range and 7.1 for

Table 1. Problems associated with small for gestational age

Short stature
Neurocognitive dysfunction
Renal function impairment
Pulmonary function impairment
Decreased bone density
Sensorineural hearing loss
Premature adrenarche/puberty/PCOS
Metabolic syndrome

PCOS, polycystic ovary syndrome.

those born shorter than normal range[18]. The mechanisms that lead to the persistence of short stature in children born SGA are not yet well understood.

Hormonal status in short SGA children

Short children born SGA usually do not have a classical GH deficiency, but instead have been found to have either low GH secretion or reduced sensitivity to GH[19]. Approximately 50%–60% of short children born SGA have either 24-hour GH profile abnormalities or subnormal responses to arginine provocation with reduced plasma insulinlike growth factor (IGF)-I and IGF-II levels which indicate GH insufficiency[19-22].

GH stimulation testing is not required to identify candidates for GH therapy among children born SGA who fail to achieve catch-up growth[23]. Additionally, GH stimulation test results do not accurately predict response to GH therapy.

GH stimulation testing is recommended when growth hormone deficiency (GHD) is suspected in a child born SGA. Signs of GHD include continued postnatal growth failure with growth velocities that result in decreasing height standard deviation scores (SDS) over time, postnatal hypoglycemia, prolonged and severe jaundice in infants, and low serum levels of IGF-I and IGF binding protein-3.

Bone age is typically delayed compare to chronological age in short prepubertal children born SGA, as SGA children have abnormal bone maturation rhythms throughout childhood. In untreated short children born SGA, a spontaneous acceleration in bone maturation and a decrease in height SDS for bone age occurs from 6 to 8 years of age. Lastly, predictions of final height based on bone age estimates have been shown to be unreliable in children born SGA who then fail to show catch-up growth[24,25]. For these reasons, bone age is not a consideration when initiating GH treatment in SGA children.

GH treatment

The aim of GH therapy is to catch up to a normal height in early childhood, maintain a normal height gain during childhood, and achieve an adult height within the normal target range.

The optimal GH dose in short SGA children is currently being debated, as shown by a recent consensus[25]. GH was approved by the Food and Drug Administration in 2001 and by the European Agency for the Evaluation of Medicinal Products in 2003. Since August, 2014, growth hormone treatment is covered by medical insurance for short children who were born SGA without catch up growth by 4 years of age (Table 2).

1. Effects of GH and factors affecting the growth response during GH therapy

Average height gain after 3 years of GH treatment ranges from 1.2 to 2.0 SD for doses of 35–70 µg/kg/day. The growth rate decrease over time in GH therapy[25]. Annual height velocity was significantly greater among children receiving GH than among untreated children during the first and second years of treatment. Untreated SGA children did not experience an increase in height velocity SDS[26]. A multicenter, phase III clinical study in Korea reported that height velocity significantly increased from 5.36± 1.59 cm/yr at baseline to 10.66±2.03 cm/yr at 6 months within the treated group[27].

Factors associated with response to GH over the first 2 to 3 years of therapy included age and height SDS at the start of therapy, midparental height, and GH dose[28].

Ranke et al.[29] reported that GH dose was the most important response predictor, accounting for 35% of growth response variability. Other predictors of growth response during the first year of treatment were age at the start of treatment, weight SDS, and midparental height SDS. In the second year of GH treatment, the final height outcome could be determined by a child's initial response to GH, which was dose dependent.

In another study, significant differences in final height based on dose were not found, between children treated with 0.033 or 0.067 mg/kg/day of GH. Positive predictors of the growth response to final height in their study were target height SDS, height SDS at the start of treatment and bone age delay at the start of treatment[30].

De Zegher et al.[31] reported that a GH dose of 0.33 mg/kg/day required 5.5 years to achieve a 2SDS increase in height, but only required 2.5 years with a dose of 0.67 mg/kg/day.

GH treatment for those with very marked growth retardation should be considered at a dose of 35–70 µg/kg/day, as these patients require rapid catch-up growth. The standard GH 'replacement' dose (i.e., the dose used to treat GHD) is insufficient for inducing catch-up growth in many short children born SGA. Age at the start of treatment was also one of the major determinants of growth; the younger the child, the greater his/her growth response to GH therapy.

2. Effect of GH on final height

Previous studies have suggested that GH treatment does not improve final height above that of controls in short children born SGA[32,33]. Contrary to those findings, Ranke and Lindberg[34] found that GH treatment in short older children born SGA can be effective in increasing final height above the predicted height and in achieving the patients' target height. Van Pareren et al.[30] reported that an average of 7.8 years of continuous treatment with GH resulted in a normalization of height during childhood and a normalization of adult height (above –2 SDS) in 85% of the patients, whereas 98% reached an adult height within their target height range in 54 short children born SGA.

3. Duration of GH treatment

De Zegher et al.[31] reported that a dose of 0.1 mg/kg/day produced a dramatic and rapid increase in height SDS over 2 years of treatment. After treatment ceased, however, height velocity decreased significantly, with a subsequent decrease in height SDS. In contrast, height SDS showed a sustained improvement in patients treated continuously with a GH dose of 0.033 mg/kg/day over 6 years.

Fjellestad-Paulsen et al.[35] studied GH therapy given at a dose of 0.47 mg/kg/wk for 3 years, before discontinuation and follow-up for an additional 5 years in 63 patients. GH therapy induced a significant catch-up in height of 2 SDS ($P<0.0001$) during the 3-year treatment period, but was followed by a decrease in height of 1 SDS 5 years after treatment was discontinued.

4. Effects of GH on metabolism

GH treatment in short children born SGA also has a positive effect on blood pressure and lipid metabolism in 79 SGA patients[36]. Before therapy, the mean body mass index (BMI) SDS of the SGA children was significantly lower than zero. During treatment, BMI SDS increased to values not significantly different from zero. This normalization of BMI was not accompanied by changes in body fat percentage.

Pretreatment systolic blood pressure SDS was significantly higher and diastolic blood pressure was significantly lower in children born SGA than in healthy age-matched children. During GH therapy, both systolic and diastolic blood pressure SDS decreased significantly. After 6 years of GH therapy, systolic blood

Table 2. GH use in short SGA children[25]

Variable	FDA-approved indication (2001)	EMEA approved indication (2003)	Korea approved indication (2014)
Age at start (yr)	2	4	4
Height SDS at start	Not stated	−2.5 SD	3 Percentile
Growth velocity before treatment	No catch-up	<0 SD for age	No catch-up
Reference to midparental height	Not stated	Height SDS>1 SD below midparental height SDS	Not stated
Dose (µg/kg/day)	70	35	35–70

GH, growth hormone; SGA, small for gestational age; FDA, Food and Drug Administration; EMEA. European Agency for the Evaluation of Medicinal Products; SD, standard deviation; SDS, standard deviation score.

pressure in the SGA children did not differ from those of the controls, and diastolic blood pressure was even lower than those of the controls. After four years of GH therapy, there were significant decreases in total cholesterol, low-density lipoprotein cholesterol, and the atherogenic index, although high-density lipoprotein cholesterol remained unchanged.

Sas et al.[37] also reported a positive effect of GH therapy on body proportions in these 79 SGA children. Height, sitting height, hand, foot length, biacromial diameter, and biiliacal diameter were measured before and during GH therapy. At the start of GH therapy, mean SDS values for all measurements were significantly lower than zero, but during 6 years of GH therapy, mean SDS for all measurements increased significantly from baseline and closer zero. There were significant improvements from baseline in the proportions of the hands, feet and biiliacal diameter in relation to height, but the biacromial diameter in relation to height did not change. None of the changes in body proportions differed significantly between the dose groups.

GH treatment also has long-term beneficial effects on muscle and adipose tissue in short children born SGA. Leger et al.[38] studied these long-term effects on muscle and adipose tissue in 14 short children born SGA during 3 years of GH therapy and observed an increase in muscle tissue mass. Adipose tissue mass decreased significantly during the first year of therapy, but increased during the second and third years of therapy.

5. Safety

Recombinant human GH has been proven to be relatively safe. High doses of up to 0.067 mg/kg/day for SGA children with growth failure are tolerated well even in young children. Treatment interruption or withdrawal as a result of adverse events is uncommon. A multicenter, phase III clinical study in Korea demonstrated the safety of GH treatment in prepubertal short SGA children[27].

GH may induce insulin resistance and hyperglycemia, and may also affect thyroid function. In patients with GHD, slipped epiphyses of the hip may occur. To date, no studies have been conducted to evaluate the interaction of GH with other medications, but no drug-drug interactions have been reported.

The effect of GH on glucose metabolism in short children born SGA is generally mild and transient. Because insulin resistance has been reported in SGA children, fasting insulin and glycosylated hemoglobin or glucose concentrations should be monitored during and after GH treatment in these patients, particularly those with risk factors such as obesity or a family history of diabetes. A French study, Sante Adulte GH Enfant study, reported increased mortality rates among adults treated with recombinant GH as children, particularly in those who had received the highest dose (above 50 μg/kg/day). Specific effects were detected in terms of death due to bone tumors or cerebral hemorrhage but not for all cancers[39].

Conclusions

GH treatment in short children born SGA is intended to achieve normal height in early childhood, maintain a normal height gain throughout childhood, and achieve an adult height within the normal target range. It is important that short children born SGA who may benefit from GH treatment be referred to a pediatric endocrinologist as early as possible. Early surveillance in growth clinics is strongly recommended for those children born SGA who have not caught up. Although high doses of up to 0.067 mg/kg/day are relatively safe for short children with growth failure, clinicians need to remain aware of long-term mortality and morbidity possibilities after GH treatment.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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