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Clinical Study

Efficacy and Safety of Percutaneous Epiphysiodesis Operation around the Knee to Reduce Adult Height in Extremely Tall Adolescent Girls and Boys

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Objective. The aim was to determine efficacy and safety of a surgical method to reduce adult height in extremely tall adolescents. *Methods*. Data for all girls ($n = 12$) and boys ($n = 9$) in our center subjected to bilateral percutaneous epiphysiodesis around the knee who had reached final height were included. Final height predictions were based on hand and wrist X-rays before surgery. *Results*. When compared to prediction, adult height was reduced by 4.1 ± 0.7 cm in treated girls ($P < .001$) and 6.4 ± 0.7 cm in treated boys ($P < .001$) corresponding to a 33.6 ± 3.4% and 33.6 ± 4.2% reduction of remaining growth, respectively. Besides mild to moderate postoperative pain reported in 9 operated individuals, no other side effects were reported. Postoperative X-rays confirmed growth plate closure and absence of leg angulations. *Conclusions*. Bilateral epiphysiodesis is an effective and safe method to reduce adult height in extremely tall girls and boys.

1. Introduction

In Sweden, a common definition of extreme tall stature is an adult height exceeding 200 cm for boys and 185 cm for girls corresponding to approximately 3 SD above the mean. Tall stature is most often caused by genetic factors (constitutional tall stature). However, an underlying disorder must always be considered in tall individuals as many of them need special medical attention. These include homocysteinuria, growth hormone excess, and various syndromes such as Klinefelter, Sotos, Marfan, and Beckwith-Wiedemann syndrome [1, 2].

Extreme tall stature is a common reason for referral to pediatric endocrinology centers in northern European countries. Patients and their families often express a strong desire for intervention aiming to reduce adult height. The treatment options for children with extreme tall stature are limited. To reduce final height (FH), boys have been treated with high-dose testosterone and girls with high-dose estradiol [3, 4]. The treatment was introduced already in 1956, but its use has decreased dramatically in the last two decades, possibly due to a change in attitude towards tall stature and concerns of long-term complications [5]. In a meta-analysis study, hormonal treatment was only found to reduce final height if initiated before a bone age of around 14 yrs in both genders [6]. It was suggested that administration of sex steroids after this age causes extra growth instead of growth inhibition.

Undesired side effects are commonly reported in patients undergoing hormonal treatment for tall stature. For boys, one of the most common complaints reported is acne. Other documented side effects are weight gain, muscle ache, gynecomastia, hypertrichosis, behavioural changes, and aggressiveness [7, 8]. For girls, side effects include nausea, headache, elevated serum triglycerides, calf cramps, and weight gain [8–10]. More serious concerns with the treatment include a possible increased risk of venous thrombosis. Studies have shown changes in coagulation parameters [11] although no studies have been able to show

an increased risk of venous thrombosis [12]. There is also a fear of a further increased risk of breast cancer [4, 9, 13] and decreased fertility [4]. One study from Australia shows that women who have been on high-dose oestrogen treatment to reduce their final height are more likely to have tried for over a year to get pregnant (relative risk 1.80, 95% CI 1.40–2.30) and to have taken fertility drugs (relative risk 2.05, 95% CI 1.34–3.04). They are also less likely to conceive in any given menstrual cycle although the possibility of conceiving at all is only slightly decreased, possibly due to the availability of fertility treatments. Because of the various side effects associated with hormonal treatment and sometimes limited efficacy, an alternative treatment modality is desired.

Surgical epiphysiodesis performed around the knee has for many years been used to treat leg length discrepancies [14]. In extremely tall boys, the use of bilateral percutaneous epiphysiodesis was recently reported to reduce adult height by approximately 5 cm when performed at a mean bone age of 13.9 years [15]. However, it is important to point out that still this is a controversial treatment as it is being performed in healthy adolescents and further supportive data are lacking.

The aim of our study was to determine the efficacy and safety of bilateral epiphysiodesis around the knee when performed to limit further growth in extremely tall adolescent girls and boys. We included radiological assessments of bone growth and bone angles and a reference group of untreated extremely tall subjects to document the efficacy and safety of bilateral percutaneous epiphysiodesis.

2. Subjects and Methods

2.1. Study Subjects. All study subjects have been followed at the Pediatric Endocrine Clinic at Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden. After approval by the local ethics committee, patients have been recruited since year 1997. All tall girls and boys who fulfilled the inclusion criteria (Table 1) were offered to undergo bilateral percutaneous epiphysiodesis around the knee. Informed consents were given by all patients who participated in the study and their parents. Until January 2009, 49 patients (21 boys and 28 girls) have undergone surgery. Out of these, 21 subjects (12 girls and 9 boys) had reached final height, and data from all these subjects are presented in this paper. All patients had been diagnosed with constitutional tall stature except three patients with Marfan syndrome and one with Klinefelter syndrome. Most of the patients were midpubertal at time of surgery, the girls generally slightly less advanced in their pubertal development (range B2–B4) than the boys (G2–G5). In the constitutionally tall patients, the midparental height (defined as the average of the parent's heights −6.5 cm for girls and +6.5 cm for boys) was calculated. Midparental height was 177.7 ± 1.9 cm in girls and 190.5 ± 1.1 cm in boys (corresponding to +1.7 SDS and +1.5 SDS, resp.). Two patients with constitutional tall stature were excluded from this calculation, one with a parent who had received hormonal treatment for tall stature and another with a parent diagnosed with Marfan syndrome.

Table 1: Inclusion criteria to be offered bilateral percutaneous epiphysiodesis.

(i) Final height prediction of at least 200 cm in boys and 185 cm in girls
(ii) Remaining predicted growth of at least 8 cm
(iii) Relatively long legs (relative sitting height below the mean)
(iv) A strong patient desire to undergo the treatment

At each occasion, height and sitting height were measured by an experienced professional using a Harpenden stadiometer. Bone age maturation was determined by two blinded experts on an X-ray film of the left hand and wrist using the atlas of Greulich and Pyle [16]. Final height predictions were made according to the Bailey and Pinneau tables [17]. To further verify the efficacy and safety of the treatment, hip-knee-ankle (HKA) angles and leg lengths (femur and tibia lengths) were measured digitally on plain X-ray films before surgery and at final height. Due to technical and practical problems, complete information for HKA-angle was only available in 15 patients and for leg length in 9 patients.

2.2. Validation of the Final Height Prediction Error in Untreated Tall Subjects. To validate the precision of our final height predictions, we recruited 17 untreated subjects (12 girls and 5 boys), all diagnosed with constitutional tall stature. They had been through a similar workup as the operated patients, including a hand X-ray but had never undergone treatment. At time of first visit, the mean age was 13.6 ± 0.4 yrs in girls and 15.2 ± 0.8 yrs in boys while the mean bone age was 12.9 ± 0.1 yrs in girls and 14.6 ± 0.6 yrs in boys. These reference subjects did not significantly differ from the study population (Table 3). The mean height at this initial workup was 175.9 ± 1.1 cm in girls and 188.5 ± 5.9 cm in boys. Based on evaluation of a hand and wrist X-ray film obtained, the final height predictions were 184.0 ± 1.0 cm and 200.7 ± 2.2 cm in girls and boys, respectively. When comparing predicted final height with achieved adult height, we found that girls were overpredicted by a mean of 0.2 ± 0.6 cm and boys overpredicted by a mean of 1.3 ± 1.8 cm.

In addition, we recruited another group of 12 young normal height adults (age 20–40 years; 11 females and 1 male) that were measured twice in a day with an eight-hour interval (at 8 am and 4 pm) with the aim to quantify the well-known reduction of height that normally occurs throughout the day. In these subjects, the mean loss in height over 8 hours was 0.7 ± 0.1 cm. When validating the final height predictions, we compensated for the calculated hourly loss in height over the day (0.092 ± 0.012 cm/hour) to correct for any error caused by a difference in time between measurements performed in individual subjects. If making this correction, final height predictions in the tall untreated girls were equal to the achieved adult heights for girls (0.1 cm) while boys were still slightly overpredicted (0.5 cm). As the mean prediction error was so small, we decided not to correct for this when calculating the efficacy of the operation in the study population.

2.3. Surgical Technique. Growth arrest was achieved by bilateral percutaneous epiphysiodesis performed under general anaesthesia. A tourniquet was applied to reduce bleeding. The growth plates of the distal femur and proximal tibia and fibula were identified using an X-ray image intensifier (C-arm). Through one cm incisions at the lateral aspects of the femoral and tibial growth plates, epiphysiodesis was performed with a drill (8 mm) and oval angulated curettes (5–7 mm). The growth plate of the fibula was curetted with a 3 mm straight oval curette through the tibial incision from an anterior direction to avoid damage to the peroneal nerve. The curettage was controlled by short snapshots with the image intensifier. Between 25% and 50% of each growth plate was removed to induce the formation of bony bridges across the physis to ensure complete elimination of growth. Curetted bone tissue was removed from the subcutaneous tissue to avoid extraosseous bone formation. Local anaesthesia was injected adjacent to the skin incisions. The total operation time was approximately 45 minutes per leg.

In the here reported patients, postoperative analgesia was supported by continuous femoral nerve blockage for 24–48 hours. Additional postoperative analgesia was achieved by oral paracetamol and nonsteroidal anti-inflammatory drugs. More recently, we have discontinued to apply femoral nerve blockage which has facilitated the postoperative mobilization with no increase in the reports of postoperative pain (data not shown).

To achieve full range of knee movement, physiotherapy and full weight bearing with crutches was initiated within 24 hours after surgery. Patients were discharged from the hospital when they were able to ambulate and bend their knees at least 90 degrees which typically occurred on the 2nd or 3rd day postoperatively. As a precaution, patients were advised to avoid strenuous physical activities for 4 weeks (no running or jumping).

2.4. Followup of Study Subjects. Twelve months postoperatively, total destruction of operated growth plates was confirmed on plain knee X-ray films. Total height, sitting height, and arm span were measured every 12 months after surgery until adult height was reached. Leg length was calculated as the difference between measured total height and sitting height. In addition, leg length was measured radiologically both preoperatively and when adult height had been reached. According to our definition, adult height was reached when the calculated growth velocity was less than 0.5 cm per year when assessed over a minimum of a 6-month interval. When adult height had been reached, each patient went through a work up which included clinical examination focusing on the efficacy and long-term safety of the treatment. In addition, plain digital X-ray films were taken of both legs to determine if any angulation (hip-knee-ankle angle) or leg length discrepancy had developed as a consequence of the previous operation.

2.5. Statistics. Results are reported as means ± SEM. Student's *t*-test was applied and when normality test failed Wilcoxon Signed Rank test was used to analyse treatment effects. The relationship between pairs of variables was assessed by Pearson's correlation. *P*-values of $< .05$ were considered statistically significant.

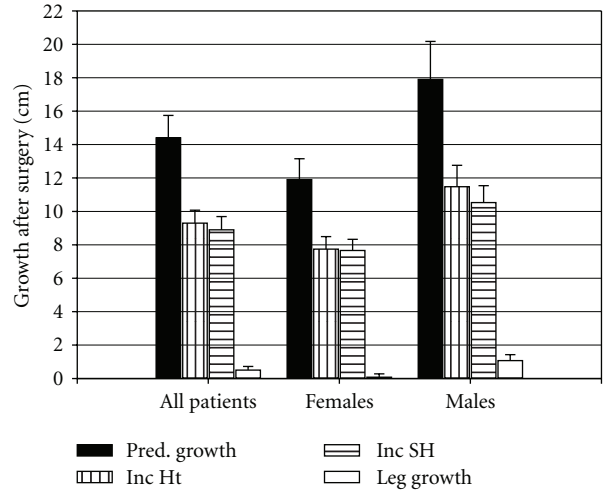

Figure 1: Predicted growth (Pred growth), increase in height (Inc Ht), increase in sitting height (inc SH), and increase in leg length (leg growth) from time of surgery.

3. Results

3.1. Baseline Characteristics of the Study Population. The baseline characteristics of individual subjects are detailed in Table 2. Average height at surgery, predicted final height, and achieved final height for the study population are shown in Table 3. Mean predicted final height at time of surgery corresponded to +3.8 ± 0.2 SDS in girls and +3.8±0.3 SDS in boys. Then, the remaining predicted growth (final predicted height subtracted by height at surgery) was 11.9 ± 1.2 cm in girls and 17.9 ± 2.3 cm in boys (Figure 1).

3.2. Treatment Effect. In patients who underwent bilateral percutaneous epiphysiodesis, the mean achieved final height was 186.4 ± 0.8 cm in girls and 199.1 ± 1.5 cm in boys (Table 3) corresponding to +3.1±0.1 SDS and +2.8±0.2 SDS, respectively. Figure 2 illustrates the distribution of height reductions versus initial predictions for all treated patients. The mean reduction of final height versus initial prediction at time of surgery was 4.1 ± 0.7 cm in girls ($P < .001$) and 6.4 ± 1.2 cm in boys ($P < .001$) corresponding to growth reductions of 33.8 ± 3.4% and 33.6 ± 4.2%, respectively (Table 3). As expected, after surgery most of the growth occurred in the upper body segment (Figure 1). The mean increment in sitting height was 7.7 ± 0.7 cm in girls and 10.4 ± 1.0 cm in boys, respectively, while the mean leg growth (increase in total height subtracted by increase in sitting height) was only 0.1 ± 0.2 cm in girls and 1.1 ± 0.4 cm in boys (Figure 1). In the patients where leg growth was assessed radiologically, mean femoral growth was 0.4 ± 0.2 cm while mean tibial growth was 0.7 ± 0.2 cm. Altogether, the men

Table 2: Clinical data for individual patients.

Patient no	CA at op	BA at op	Puberty at op	Height at op	FPH at op	FH	PFH-FH	Diagnosis
Females								
1	14.7	12.2	B2	179.7	191.7	186.9	4.8	CTS
2	13.8	12.8	B3	179.5	189.9	183.9	6.0	CTS
3	13.6	13.0	B2	182.2	190.7	187.8	2.9	CTS
4	13.5	13.0	B3	178.0	186.0	182.9	3.1	CTS
5	12.5	10.2	B2	176.0	199.8	189.8	10.0	CTS
6	13.0	12.7	B4	181,1	191.0	189.5	1.5	CTS
7	13.1	12.0	B2	180.0	193.5	189.7	3.8	CTS
8	11.6	12.6	B3	181.0	189.9	187.0	2.9	CTS
9	12.7	12.5	B3	175.7	185.4	182.8	2.6	Marfan
10	13.4	12.6	B2	177.3	190.2	184.9	5.3	CTS
11	11.8	11.5	B2	173.6	188.7	183.5	5.2	Marfan
12	13.7	12.5	B3	180.0	189.7	188.2	1.5	CTS
Males								
13	16.5	14.3	G5	192.4	205.1	201.2	3.9	CTS
14	15.2	14.0	G3	183.1	196.0	191.7	4.3	CTS
15	14.2	14.5	G4	188.4	198.6	198.3	0.3	CTS
16	14.7	12.9	ND	185.5	211.2	200.5	10.7	CTS
17	13.7	14.2	G5	199.5	212.8	208.5	4.3	CTS
18	13.7	13.9	G3	187.8	207.0	199.0	8.0	CTS
19	14.5	14.1	G4	189.0	204.0	197.5	6.5	CTS
20	12.3	12.3	G1	175.3	205.5	195.3	10.2	Marfan
21	12.2	13.8	G5	187.9	209.6	200.2	9.4	Klinfelter

Chronological age (CA, yrs), bone age (BA, yrs), puberty (Tanner pubertal stage, breast (B) for girls and gonad (G) for boys), height (cm), and predicted final height (PFH, cm) at time of epiphysiodesis operation (op). Final height (FH, cm) and individual diagnosis (constitutional tall stature (CT), Marfan Syndrome (Marfan), and Klinefelter Syndrome (Klinefelter)).

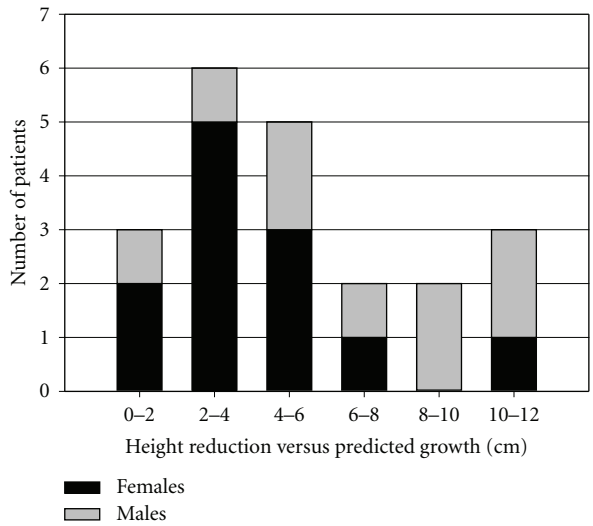

Figure 2: Distribution of patients based on height reductions versus predictions in girls and boys.

leg growth (femur + tibia growth) from surgery until final height was 1.2 ± 0.1 cm ($n = 9$) as measured by X-ray.

In boys, final adult height was reduced by 3.9–10.7 cm except for one single patient who had a reduction of only 0.3 cm. In this patient, the upper body growth after surgery was 9.0 cm while leg growth was only 0.9 cm. Except for one boy with Marfan syndrome (subject no. 20; Table 2), no patient showed a leg growth exceeding 1.2 cm after surgery. In this boy, leg growth was 3.3 cm while his upper body segment increased by 16.7 cm resulting in a 10.2 cm reduction of adult height compared to the initial prediction. An X-ray obtained 12 months after surgery clearly demonstrated that his distal tibia growth plates were still completely open while his operated proximal tibia and distal femur growth plates were, as expected, fused. When excluding patients with primary growth disorders (three with Marfan and one with Klinefelter syndrome), mean leg growth after surgery was only 0.4 ± 0.2 cm and if analyzed separately 0.0 ± 0.2 cm in girls and 0.9 ± 0.3 cm in boys.

Figure 3 shows a clear negative correlation between bone age at time of surgery and height reduction, a correlation which was slightly stronger in boys ($r = -0.818$; $P < .01$) than in girls ($r = -0.769$, $P < .01$). One of the female patients was operated at an early bone age (10.1 yrs). If this patient is excluded, the negative correlation between bone age and final height reduction does not remain significant in girls.

3.3. Effect on Body Proportions. All operated girls except one (Figure 4(a)) and all boys except two (Figure 4(b)) had a

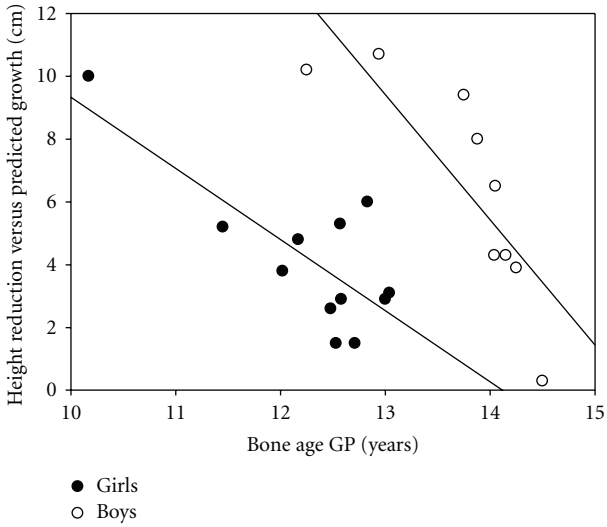

Figure 3: Reduction of predicted final height as a function of bone age at time of surgery. In both girls and boys, a negative correlation was found between bone age and reduction of predicted final height.

relative sitting height below or well below the mean for age showing that the subjects had relatively long legs at time of surgery. The relative sitting height (SH) increased in every treated girl (Figure 4(a)) and boy (Figure 4(b)). In girls, the mean relative SH was 51.9 ± 0.3% at FH versus 49.9 ± 0.3% at operation ($P < .001$). In boys, the relative SH at FH was 52.3 ± 0.4% versus 50.0 ± 0.3% at operation ($P < .001$). In the reference population, the mean relative SH at FH is 52.4% in girls and 51.5% in boys [19]. Thus, in our operated patients, relative SH at FH was still below the mean in girls and for boys just slightly above the mean. For girls, average sitting height percentage was 52.1 in patients treated before and 51.8 for those treated after a bone age of 12.5 yrs. For boys, the sitting height percentage was 51.8 in patients treated before and 52.7 for those treated after a bone age of 14.0. From time of surgery to final height, mean arm span increased 3.2 ± 1.6 and 4.0 ± 1.2 cm more than height in girls ($n = 9$) and boys ($n = 7$), respectively.

3.4. Safety. No serious side effects were reported in our study. One patient had a postoperative superficial cutaneous infection which did not require treatment with antibiotics. Nine patients reported postoperative pain from the site of surgery and received oral analgesics (2–14 days). No patient experienced pain after the first two postoperative weeks.

Leg length discrepancy did not change significantly between time of surgery until final height was achieved ($n = 10$; $P = .560$). The mean leg length difference before operation was 0.4 ± 0.1 cm (range 0.0–0.9 cm) and at final height 0.3 ± 0.1 cm (0.0–1.0 cm). To verify if any knee angulations developed after surgery, radiologic measurements of the Hip-Knee-Ankle (HKA) angle were performed before surgery and at final height. Between these two occasions, the HKA angle was increased in seven patients (0.5–5.0 degrees)

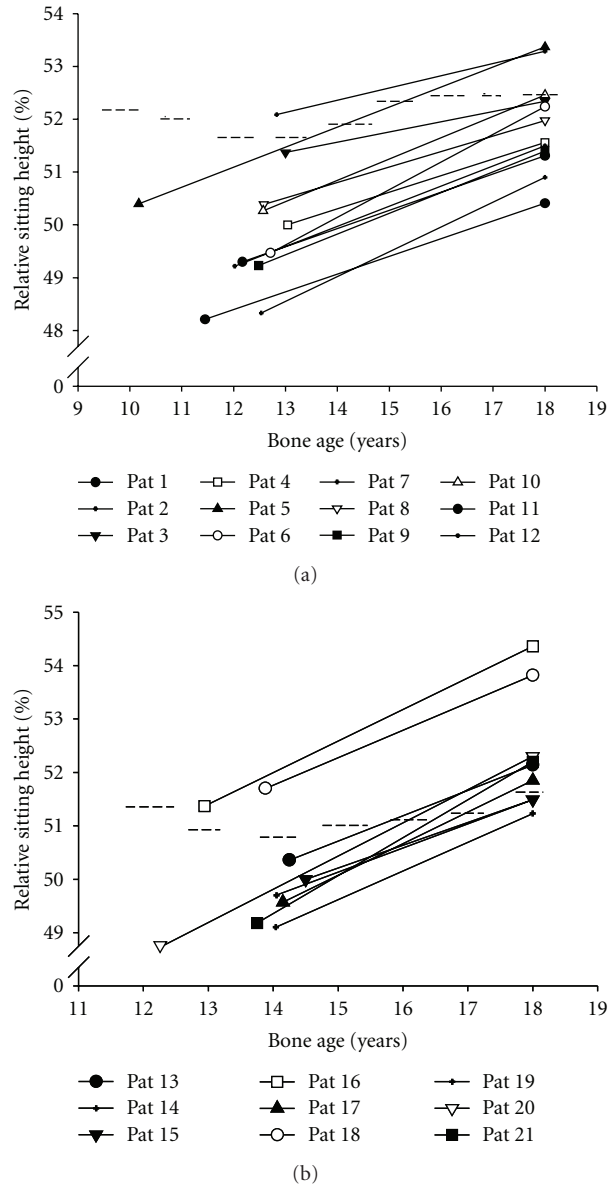

Figure 4: Relative sitting height as a function of bone age in girls (a) and boys (b). For individual patients, the symbols illustrate the relative sitting height and bone age at time of surgery and at adult height. The hatched horizontal lines indicate the mean relative sitting heights for the normal population.

while decreased in ten (0.5–5.0 degrees). In four of these patients, the HKA angle was increased in one leg while decreased in the other. None of them needed intervention or experienced physical problems related to the surgery.

4. Discussion

We here report that bilateral percutaneous epiphysiodesis performed around the knee effectively inhibits further leg growth when performed in extremely tall adolescent girls and boys. The operation was more effective when performed at

Table 3: Clinical data for females and males.

	CA at op (yrs)	BA at op (yrs)	Height at op (cm)	PFH at op (cm)	FH (cm)	PFH-FH (cm)
Females	13.1 ± 0.2	12.3 ± 0.2	178.7 ± 0.7	190.5 ± 1.1	186.4 ± 0.8[a]	4.1 ± 0.7
Males	14.1 ± 0.4	13.8 ± 0.2	187.7 ± 2.2	205.5 ± 1.8	199.1 ± 1.5[a]	6.4 ± 3.5

Chronological age (CA), bone age (BA), and predicted final height (PFH) at operation (op). Final height (FH). Means ± SEM. [a]$P < .001$ versus PFH at operation.

an early bone age. We found the procedure to be safe and no significant side effects were reported.

We here document the efficacy and safety of epiphysiodesis in both girls and boys. Previously the only report of long-term outcome of this procedure has been in boys. The height reduction in our male patient group is in agreement with what was previously reported [15]. We have not only based our data on auxological measurements but also verified the efficacy and safety radiologically. To further strengthen the accuracy of the final height predictions, a validation cohort was recruited.

In both girls and boys, bilateral percutaneous epiphysiodesis reduced the predicted remaining growth from time of surgery by approximately one third. When reviewing studies of hormonal treatment, epiphysiodesis seems to be more efficient in reducing final height. In girls treated at a bone age of 12.5 yrs, the height reduction is around 2 cm with hormonal treatment and around 4 cm with epiphysiodesis [6]. In boys treated at a bone age of 14 yrs, epiphysiodesis results in a final height reduction by around 6 cm whereas hormonal treatment at this bone age results in no height reduction at all according to a meta-analysis [6]. Our results showed that epiphysiodesis was efficient in reducing final height in all patients except for one boy where we believe his predicted remaining growth was underestimated. This assumption is based on the fact that the growth of his upper body (9.0 cm) far exceeded his leg growth (0.9 cm) suggesting that the intervention was indeed effective also in this patient.

With regards to safety, we monitored for short-term side effects such as postoperative infections, pain, or discomfort as well as long-term side effects including any hip-knee-ankle angulations, leg length discrepancies, or abnormal body proportions. The only side effects reported were mild to moderate postoperative pain and one superficial cutaneous infection. Our findings are in agreement with a previous study of epiphysiodesis where no serious side effects were reported either [15]. Although no serious complications occurred, it should be noted that this is an invasive procedure in otherwise healthy individuals. Failure of epiphysiodesis secondary to insufficient ablation of the physis has indeed been reported by others [18]. Therefore, careful diagnostic preoperative evaluation is essential, and the treatment should be performed in a center of expertise ensuring the long-term followup. Regarding body proportions, relative sitting height at final height was indeed closer to the normal than before surgery when being compared to normative tables for the general population [19]. The reason for this is that tall stature is usually characterized by relatively long legs [20]. In most girls, the sitting height percentage remained below the mean at final height. In contrast, most boys had a sitting height percentage which was above the normative population, and in two of them this was more pronounced, most likely linked to the fact that their sitting heights were above the mean already at the time of surgery. At final height, none of the treated patients expressed dissatisfaction with their body proportions. However, an increase in relative sitting height is to be excpected and should be considered before treatment decision is made. We do not believe that the surgical treatment will lead to any long-term side effects in contrast to hormonal treatment for which fear has been raised of side effects such as reduced fertility [4] and breast cancer [11, 13]. Other side effects that have been associated with hormonal treatment, such as hypertension and thrombosis [11], were not seen in our operated patients. Therefore, we regard surgery as the treatment of choice in extremely tall patients with high blood pressure and/or a family history of venous thrombosis.

Final height predictions are known to be imprecise estimates of remaining growth. The most widely used method for prediction of final height was devised by Bayley and Pinneau (BP method). This method is routinely used in clinical practise [6]. At time of surgery, most of our patients were in midpuberty with a mean age of 13.1 ± 0.9 yrs in girls and 14.1 ± 1.4 yrs in boys. A previous study has shown that the mean height prediction errors (BP method) at these ages are 0.5 ± 2.2 cm in girls (13 yrs) and 2.7 ± 2.9 cm in boys (14 yrs) [6].

In order to reduce any prediction errors, all X-ray images were read by two blinded observers. In an attempt to quantify the potential errors of these predictions, we recruited an untreated reference population of extremely tall females and males. This validation clearly demonstrated that the predication errors were so small that we could ignore it when calculating the efficacy of the treatment. It is important to point out that the untreated reference group did not differ significantly from the treated group, although not being randomly selected. It would of course have been optimal to include a randomized untreated control group, but this was not possible for technical reasons. Nevertheless, the efficacy of the operation was confirmed by radiological leg measurements which is a very reliable method to assess bone growth.

5. Conclusions

Our data suggest that bilateral percutaneous epiphysiodesis is an efficient and safe method to reduce adult height in extremely tall adolescents. The intervention should not be performed too late, preferably at a bone age not exceeding twelve and a half years in girls and fourteen years in boys.

We recommend that a treatment decision is taken before girls have reached a height of 170 cm and boys 185 cm. Hereby, the expected growth reduction will exceed 5 cm as long as the predicted final height is at least 185 cm in girls and 200 cm in boys. The patients should preferably have preoperative evaluation, treatment, and followup in a specialized center with expertise in pediatric endocrinology and pediatric orthopaedic surgery. Further studies are desired to document the efficacy and safety of this relatively new procedure in larger patient groups.

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