The etiology of short stature affects the clinical outcome of lower limb lengthening using external fixation
A systematic review of 18 trials involving 547 patients

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Background and purpose — Distraction osteogenesis (DO) has been used to gain height in short statured individuals. However, there have been no studies comparing the clinical outcome of limb lengthening based on the etiology of the short stature. We assessed whether different underlying diagnoses are associated with varied clinical outcomes in these patients.

Methods — We performed a systematic review of the literature pertaining to lower limb lengthening using external fixation for short stature. Clinical outcomes including amount of lengthening, healing index (HI), and complications based on the underlying diagnosis for the short stature were documented.

Results — 18 clinical studies were included, with 547 patients who underwent 1,581 lower limb segment lengthening procedures. Mean follow-up was 4.3 years. The average age at lengthening was less for individuals with achondroplasia/hypochondroplasia (A/H) (14.5 years) than for those with Turner’s syndrome (TS) (18.2 years) or with constitutional short stature (CSS) (21.7 years). Mean height gained was greater in patients with A/H (9.5 cm) than in those with TS (7.7 cm) or CSS (6.1 cm) group. The HI was better in A/H (30.8 days/cm) and CSS (32 days/cm) than in TS (45.1 days/cm). The reported complication rate per segment was lower for A/H (0.68) and TS (0.71) than for CSS (1.06).

Interpretation — Patients with A/H tolerated larger amounts of lengthening with fewer complications than those with other diagnoses.

Distraction osteogenesis (DO) uses a corticotomy or osteotomy to allow formation of new bone in the gap created by controlled distraction of the bone segments. In 1905, Codivilla proposed limb lengthening through distraction (Codivilla 2008), and this concept was reintroduced in 1969 by Ilizarov (Ilizarov and Deviatov 1969) and in 1977 by Wagner (1977) using external fixation (EF). Since then, DO has been used to address non-unions, skeletal defects, and limb deformities, including limb length discrepancy (Aronson 1997, Liu et al. 2011).

More recently, this surgical modality has been used to increase standing height in individuals of short stature (Koczewski et al. 2002). Although there are several challenges associated with DO such as length of treatment, the psychological consequences of treatment, and permanent complications, with advances in DO—including the availability of newer implants and techniques—more individuals with a variety of underlying diagnoses will undergo limb lengthening. However, to our knowledge, there have been no large comparative studies on the clinical outcome of lower limb lengthening for short stature based on the underlying diagnosis.

We performed a systematic review of the literature on lower limb lengthening and assessed whether there were any differences in the reported clinical parameters, such as lengthening percentage (LP) and healing index (HI), based on the etiology of short stature. From previous literature (Paley 1988), we hypothesized that patients with achondroplasia and hypochondroplasia would have undergone greater degrees of lengthening with fewer reported complications than those with other diagnoses for their short stature.

Patients and methods

Search strategy and criteria
On October 18, 2012, we searched PubMed, MEDLINE, the Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane Library for articles published between 1950 and 2012. The search terms used were “stature lengthening”, “height lengthening”, “limb lengthening”, and “distraction osteogenesis”. After discarding all duplicate articles and restricting the search to manuscripts available in the English
language and pertaining to human subjects, 2 of us (SJK, WP) reviewed each remaining abstract manually. The search was further narrowed to include only those articles that focused on bilateral lower limb lengthening for short stature using EF only and that included the patient’s underlying diagnosis and limb segment(s) (femur/tibia) that were lengthened (Figure). An orthopedic surgeon (SJK) and an orthopedic resident (WP) independently assessed the eligibility of all relevant studies based on our inclusion criteria. Disagreements between the reviewers were resolved by discussion. The inclusion criteria included (1) full-length articles published from January 1, 1950 to August 18, 2012, (2) articles written in the English language about human subjects, (3) cases of lengthening using EF only, and (4) articles that documented complications. The exclusion criteria included (1) cases of lengthening over nail (LON), (2) review articles focusing on the technique of lengthening, (3) articles without clinical outcomes such as LP and HI, and (4) evaluation of any segment other than the lower limb (for example, lengthening of the humerus). In order to minimize bias related to the technique of DO, we excluded patients who had undergone lengthening involving intramedullary (IM) nails, with or without EF. Limits regarding the number of patients in each study or the minimum duration of follow-up were not used. All study designs of levels I–IV were included. Bibliographies of the studies included were also searched to identify other relevant studies. Based on the above search criteria, 18 clinical studies were available for the final analysis (Table 1).

**Data extraction**

Relevant information such as level of evidence, patient demographics, limb segment lengthened, preoperative height, device(s) used for limb lengthening, amount of lengthening, LP (final regenerate length divided by initial bone length, multiplied by 100) (Givon et al. 2001), HI (number of days to union divided by the final regenerate length in cm) (Kim et al. 2011), any reported complications, and mean follow-up period were extracted from each of these studies. Clinical outcome measures varied among the studies.

The patient’s underlying diagnosis was categorized under one of the following categories: achondroplasia/hypochondroplasia (A/H), Turner’s syndrome (TS), and constitutional short stature (CSS). The patients with body dysmorphism/normal height were excluded because most of them underwent LON. Achondroplasia and hypochondroplasia were integrated in 1 group because it is often difficult to clearly discriminate achondroplasia patients from hypochondroplasia patients clinically, and patients with these 2 diagnoses are reported together in most reports (Ng et al. 2003). If there was a chance that the same patients (patients who were reported in 2 or more studies and treated by the same surgeon over a similar operation period) had been included more than once in the present study, only the patients in the study with a larger cohort were included for data extraction and statistical analysis in order to minimize any potential for sampling bias.

It was difficult to use a uniform classification of complications due to reporting inconsistencies. The study by Paley (1990) was cited by several research groups (Vaidya et al. 2006, Park et al. 2008, Kim et al. 2012c), but then not used to evaluate the patients noted in their articles. We therefore evaluated the total numbers (sum) of complications (problems, obstacles, and sequelae) (Eralp et al. 2010, Kim et al. 2011) and complication rate per segment. It was also challenging to divide complications into problems and obstacles, as these were not consistently reported. Thus, we documented only numbers of sequelae (permanent complications) defined.
as all problems during lengthening that were not resolved by the end of treatment (Eralp et al. 2010, Kim et al 2011).

Statistics

We analyzed data using SPSS software. The chi-square test was used to evaluate differences in the complication rates and sequelae between groups. Any p-value of < 0.05 was regarded as significant. It was not possible to conduct a meta-analysis due to the heterogeneity of the reports. An I² value of 75% was indicated according to the test statistic for evaluation of heterogeneity (Higgins et al. 2003).

Results

18 level-IV studies met our inclusion criteria, yielding data on 547 subjects who underwent 1,581 lower limb segment lengthening procedures. No level-I or -II studies were identified in our search. While the underlying diagnoses, limb segments lengthened, and devices used for lengthening were available for all subjects, other variables such as patient age, sex, preoperative height, and length gained were not found on a consistent basis for all studies. 7 of the 18 studies dealt with tibial lengthening only (Cattaneo et al. 1988, Noonan et al. 1997, McAllister et al. 1999, Hahn et al. 2003, Catagni et al. 2005, Vaidya et al. 2006, Park et al. 2008), 2 studies (Venkatesh et al. 2009, Kim et al. 2012a) dealt with femoral lengthening alone, and the remaining 9 studies included patients undergoing combined tibial and femoral lengthening procedures. The average age of the patients at surgery was 16.3 (4–47) years and the mean follow-up time was 4.3 (0.8–16) years. Two-thirds of the patients (367/547) had underlying diagnoses of A/H and underwent the first lengthening procedure between 4 and 35 years of age (Table 2).

Based on the information available, the average age at lengthening was less for individuals with A/H (14.5 years) than for those with TS (18.2 years) or CSS (21.7 years). The mean gain in height was greater in patients with A/H (9.5 cm) than in patients with TS (7.7 cm) or CSS (6.1 cm). The HI ranged from 24 to 67 days/cm. It was also better in patients with A/H (31 days/cm) and CSS (32 days/cm) than in those with TS (45 days/cm) (Table 3).

As noted previously, most studies reported untoward events and complications inconsistently. 805 “complications” were reported for 1,057 segments, with 0.76 complications reported per lengthened segment (Table 4). In 2 studies (Cattaneo et al. 1988, Aldegheri and Dall’Oca 2001), the distribution of complications among the patients was reported but the sum of complications was not reported. The complication rate per segment lengthened was lower for A/H (0.68) than for TS (0.71) or CSS (1.06) (p < 0.001). Sequelae were seldom reported, yet occurred in 19 segments, 5 segments, and 4 segments, respectively, with pooled percentages of 1.7% (19/1,111 segments), 2.1% (5/234 segments), and 1.7% (4/236 segments) (Table 5). The rate of sequelae was similar between groups.

Discussion

While many authors have reported on limb lengthening for increasing standing height (Park et al. 2008, Kim et al 2009, 2012b, Lie and Chow 2009), there is limited information on whether there are any differences in outcome based on the patient’s underlying etiology.

Despite the challenges with heterogeneity of the patients, lack of a consistent method of assessment, and reporting of patient-centered outcomes, we were able to gather some clinically relevant information regarding lower limb lengthening.
for stature by pooling the extracted data from the existing literature. Lower limb lengthening for increasing stature was reported most often (67%) for patients with A/H (Kim et al. 2012b). These patients also appeared to undergo the greatest amount of lengthening, to heal faster, and to have fewer reported complications than individuals with other diagnoses undergoing stature lengthening. Stature lengthening in patients with TS is more challenging due to the numerous possible medical conditions including cardiovascular, renal, and endocrine abnormalities and also learning disabilities (Gravholt 2004); thus, the indications for limb lengthening may be more limited. While patients with CSS are generally healthy, due to normal muscle to bone length ratio, these individuals can be more predisposed to development of soft tissue contractures following limb lengthening (Schoenau et al. 2004). It has been suggested that patients with achondroplasia tolerate lengthening very well because of their ligament and soft tissue laxity, and their muscle length exceeds bone length before lengthening (Paley 1988). Lengthening of more than 30% was often reported in A/H patients (Aldegheri et al. 1988, McAllister et al. 1999, Venkatesh et al. 2009, Devmurari et al. 2010). In the pooled analysis, the mean gain in height (10cm) and LP (36%) was greater in patients with A/H than in patients with other diagnoses. The HI was also better in patients with A/H and CSS than in those with TS.

Complications arising from DO can be severe, with long-term residuals. Recently, in a separate study that was not included in our analysis (due to lack of documented complications), over half of skeletally immature patients with achondroplasia who underwent DO for stature lengthening following limb lengthening (Schoenau et al. 2004). It has been suggested that patients with achondroplasia tolerate lengthening very well because of their ligament and soft tissue laxity, and their muscle length exceeds bone length before lengthening (Paley 1988). Lengthening of more than 30% was often reported in A/H patients (Aldegheri et al. 1988, McAllister et al. 1999, Venkatesh et al. 2009, Devmurari et al. 2010). In the pooled analysis, the mean gain in height (10cm) and LP (36%) was greater in patients with A/H than in patients with other diagnoses. The HI was also better in patients with A/H and CSS than in those with TS.

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### Table 3. Amount of lengthening and healing index

|                | A/H a | TS b | CSS c | Total (average) | No. of patients included | Studies not included |
|----------------|-------|------|-------|-----------------|--------------------------|---------------------|
| Mean length gained per limb in cm (range) | 9 (6–12) | 8 (6–9) | 6 (4–9) | 9 (4–12) | 547 | None |
| Mean percentage increase per limb (range) | 36 (20–53) | 26 (10–41) | 18 (7–30) | 32 (7–53) | 319 | Cattaneo et al. 1988, Catagni et al. 2005, Aldegheri and Dall’Oca 2001, Noonan et al. 1998, Ng et al. 2003, Bidwell et al. 2000 |
| Healing index in days/cm (range) | 31 (24–41) | 45 (31–57) | 32 (30–67) | 33 (24–67) | 407 | Aldegheri and Dall’Oca 2001, Bidwell et al. 2000 |

a Achondroplasia/hypochondroplasia  
b Turner’s syndrome  
c Constitutional short stature

### Table 4. Reported complications for limb lengthening

|                | A/H a | TS b | CSS c | p-value | Total | Studies not included |
|----------------|-------|------|-------|---------|-------|---------------------|
| Complications/total segment (%) | 487/707 (68) | 109/154 (71) | 209/196 (106) | < 0.001 | 805/1,057 (76) | Cattaneo et al. 1988, Aldegheri and Dall’Oca 2001 |
| Sequelae/total segment (%) | 19/1,111 (1.7) | 5/234 (2.1) | 4/236 (1.7) | 0.9 | 28/1,581 (1.8) | None |

a Achondroplasia/hypochondroplasia  
b Turner’s syndrome  
c Constitutional short stature

### Table 5. Reported sequelae of limb lengthening

|                | A/H a | TS b | CSS c | Total |
|----------------|-------|------|-------|-------|
| Stiff ankle | 11 | 3 | 2 | 16 |
| Residual peroneal nerve paralysis | 2 | 0 | 0 | 2 |
| Necrosis of the femoral head | 0 | 2 | 0 | 2 |
| Knee valgus | 3 | 0 | 0 | 3 |
| Ankle valgus | 3 | 0 | 1 | 4 |
| Septic arthritis | 0 | 0 | 1 | 1 |
| Total no. of sequelae | 19 | 5 | 4 | 28 |

a Achondroplasia/hypochondroplasia  
b Turner’s syndrome  
c Constitutional short stature
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