■ CHILDREN'S ORTHOPAEDICS

Early and late fracture following extensive limb lengthening in patients with achondroplasia and hypochondroplasia

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Two types of fracture, early and late, have been reported following limb lengthening in patients with achondroplasia (ACH) and hypochondroplasia (HCH).

We reviewed 25 patients with these conditions who underwent 72 segmental limb lengthening procedures involving the femur and/or tibia, between 2003 and 2011. Gender, age at surgery, lengthened segment, body mass index, the shape of the callus, the amount and percentage of lengthening and the healing index were evaluated to determine predictive factors for the occurrence of early (within three weeks after removal of the fixation pins) and late fracture (> three weeks after removal of the pins). The Mann-Whitney U test and Pearson's chi-squared test for univariate analysis and stepwise regression model for multivariate analysis were used to identify the predictive factor for each fracture. Only one patient (two tibiae) was excluded from the analysis due to excessively slow formation of the regenerate, which required supplementary measures. A total of 24 patients with 70 limbs were included in the study.

There were 11 early fractures in eight patients. The shape of the callus (lateral or central callus) was the only statistical variable related to the occurrence of early fracture in univariate and multivariate analyses. Late fracture was observed in six limbs and the mean time between removal of the fixation pins and fracture was 18.3 weeks (3.3 to 38.4). Lengthening of the tibia, larger healing index, and lateral or central callus were related to the occurrence of a late fracture in univariate analysis. A multivariate analysis demonstrated that the shape of the callus was the strongest predictor for late fracture (odds ratio: 19.3, 95% confidence interval: 2.91 to 128). Lateral or central callus had a significantly larger risk of fracture than fusiform, cylindrical, or concave callus.

Radiological monitoring of the shape of the callus during distraction is important to prevent early and late fracture of lengthened limbs in patients with ACH or HCH. In patients with thin callus formation, some measures to stimulate bone formation should be considered as early as possible.

Cite this article: ***Bone Joint J*** **2014;96-B:1269–73.**

Achondroplasia (ACH) and hypochondroplasia (HCH) are relatively common skeletal dysplasias with disproportionate rhizomelic shortening of the limbs caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (FGFR3).[1-4] Limb lengthening has been used for some patients with these disorders to improve not only the psychological and emotional state but also the quality of life of the patient.[5,6] However, this treatment remains controversial.[7,8] Increasing the magnitude of lengthening is associated with an increase in complications such as premature physeal closure, adjacent joint contractures and fractures.[8-10] A fracture may lead to further surgical intervention and prolonged treatment. Despite careful assessment of healing at the time of removal of the fixation devices, the incidence of fracture remains high, especially in patients undergoing progressive limb lengthening.[11]

Simpson and Kenwright[11] reviewed 173 patients undergoing limb lengthening and recorded that fractures were either early, occurring within a few weeks of removal of the fixator, or late, occurring with the development of deformity several months after the fixator had been removed. In deciding the timing of removal of the fixator and subsequent management, it is important to determine the factors that predispose to these two types of fracture. In this study, we retrospectively reviewed the results of lower limb lengthening for patients with ACH or HCH and analysed the factors influencing the occurrence of early and late fractures.

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doi:10.1302/0301-620X.96B9.33840 $2.00

Bone Joint J 2014;96-B:1269–73.
Received 24 January 2014; Accepted after revision 16 June 2014

Table I. Categorical and continuous variables of 70 lengthened segments in 24 patients

Categorical variables*	Number of limbs (patients)
Gender (male/female)	30/40 (11/13)
Disease (ACH/HCH)	62/8 (21/3)
Bone (femur/tibia)	26/44
BMI (≤ 25/> 25)	48/22 (15/9)
Healing index (< 50/≥ 50)	62/8
Continuous variables	Mean (standard deviation)
Age at operation years	14.6 (4.0) (8 to 24)
Amount of lengthening cm	9.2 (1.3)
Percentage lengthening	44.7 (13.2)

*ACH, achondroplasia; HCH, hypochondroplasia; BMI, body mass index

Patients and Methods

Patients with ACH or HCH who underwent lengthening of the lower limbs, with or without simultaneous correction of deformity, at our hospital between 2003 and 2011 and were followed-up for at least 12 months after removal of the fixation pins were included in this study. The diagnosis was made by the characteristic clinical and radiological features and/or FGFR3 genetic studies. We identified 72 lengthening procedures in 25 patients. One patient (two tibiae) required bone grafting and internal fixation due to extremely poor regenerates. As the healing index of this patient could not be evaluated he was excluded, leaving 70 limbs in 24 patients for evaluation, 21 with ACH and three with HCH.

All patients underwent bilateral tibial lengthening. Two were initially treated elsewhere and their tibial analysis was not included. A total of 13 patients (26 femora) underwent bilateral sequential femoral lengthening. Genu varum of > 10° was corrected during tibial lengthening in six patients (12 tibiae). Categorical and continuous variables of the patients are presented in Table I.

All lengthening was done with a percutaneous osteotomy and the use of a monolateral external fixator (DynaFix rail deformity system, EBI LP, Parsippany, New Jersey). After an initial delay of seven to 14 days, gradual distraction of 0.5 mm twice daily, with or without gradual correction of the deformity, was commenced. The rate of distraction was adjusted so that it did not impair the continuity of the callus on the radiographs. No post-operative immobilisation was used and weight-bearing was encouraged, as tolerated, with the aid of crutches. Distraction was continued until disturbance of gait due to joint stiffness in the lower limbs had become obvious. After distraction was completed, the device was loosened to allow dynamisation of the regenerate as it matured. The decision to remove the fixator was made as a result of at least three paediatric orthopaedic surgeons' consensus (HK, KM, MM), based on the radiological principles of Fischgrund, Paley and Suter[12] which require three of four continuous cortices to have become > 2 mm thick. Initially the frame was removed, leaving the fixation pins *in situ*. After a further one to two weeks, in the absence of fractures or bending at the regenerate, the pins were also removed. All operations and post-operative management were performed by or under the direct supervision of the senior author (HK).

The fractures were described either as early, occurring either during the period of fixation or within three weeks of the pins being removed, or late, occurring > three weeks after the pins had been removed. Gender, age at surgery, lengthened segment, body mass index (BMI), the shape of the regenerate callus, the amount and percentage of lengthening, and healing index were evaluated to determine the predictive factor for the occurrence of fractures. The BMI at the time of surgery was documented, and patients were categorised as having normal weight (BMI between 18.5 kg/m^2 and 25 $kg\ m^2$), or being overweight (BMI > 25 kg/m^2). The shape of the callus was classified into five groups; fusiform (regenerate wider than the original bone), cylindrical (with the same width as the original bone), concave (narrower than the original bone), lateral (mainly on one side of the distraction gap), and central (a thin pillar), based on the width of the callus at the time of removal of the fixator.[13] The total length gained was determined from radiographs taken before the distraction and immediately after removal of the fixation pins, and adjusted for the effect of magnification. The healing index was calculated by dividing the duration of the external fixation (days) by the extent of lengthening (cm) obtained. The distribution of fractures was noted according to the Simpson and Kenwright classification:[11] type 1: fractures within the regenerate, type 2: fractures of the bone/regenerate interface, type 3: fractures at a distance from the callus in the same bone and type 4: fractures of another segment of bone.

Statistical analysis. Continuous variables were compared by the nonparametric Mann–Whitney U test and categorical variables by the Pearson's chi-squared test. Finally, independent multivariate predictors for the occurrence of early or late fractures were identified using logistic regression in which all variables with a p-value of < 0.20 from the univariate analysis were entered into a stepwise model for the selection of the explanatory variables. The likelihood ratio, using the chi-squared test, was used to determine the significance of each predictor or possible two-way interactions among variables. Significant predictors of outcome were analysed by calculating the maximal likelihood odds ratio (OR) with 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant. Data analysis was performed using JMP version 9 software (SAS Institute, Cary, North Carolina).

Table II. Details of 11 early fractures in eight patients

Case	Gender	Age (yrs)	Bone	Site of fracture	Days after frame removal	Days after screw removal	Callus shape	Length (cm)	Length (%)	Healing index (days/cm)	Treatment
1	M	13	T	Type 2	-	2	Central	10	48.5	23.3	Cast
2	M	20	F	Type 1	1	-	Cylindrical	8.8	39	21.6	Re-fixation
3	M	19	F	Type 1	-	5	Cylindrical	6.5	19.6	24.6	Traction
4	F	17	T	Type 1	-	7	Lateral	9.2	46.3	50.3	Cast
5	F	11	T	Type 1	4	-	Central	9.4	67.1	49.8	Re-fixation
		11	T	Type 2	3	-	Concave	9.3	66.4	35.3	Re-fixation
		13	F	Type 2	-	1	Cylindrical	10	50	27.2	Cast
6	M	15	T	Type 1	3	-	Concave	10	45.5	54	Re-fixation
7	M	10	T	Type 2	-	3	Cylindrical	10	46.3	30.7	Cast
		10	T	Type 2	1	-	Lateral	11	52.6	22.2	Op (irrigation, re-fixation)
8	M	14	T	Type 1	1	-	Lateral	8.5	35.4	53.1	Re-fixation

M, male; F, female; T, tibia; F, femur; Op, operation

Table III. Details of six late fractures in six patients

Case	Gender	Age (yrs)	Bone	Site of fracture[11]	Days after screw removal	Callus shape	Length (cm)	Length (%)	Healing index (days/cm)	Treatment
1	M	13	T	Type 1	126	Central	10	48.5	23.3	Cast
2	M	11	T	Type 1	167	Concave	8.8	46.8	31.7	Cast
3	F	13	T	Type 1	23	Cylindrical	12	68.2	22.7	Brace
4	F	17	T	Type 2	89	Lateral	9.2	46.3	50.3	Cast
5	M	15	T	Type 1	269	Lateral	10	45.5	54	Crutches
6	F	15	T	Type 1	92	Lateral	8.5	46.2	56.8	Crutches

M, male; F, female; T, tibia; F, femur

Results

The mean follow-up was 4.6 years (1.7 to 9), and the mean lengthening was 9.2 cm (6 to 12), which resulted in a mean proportional lengthening of 44.7% (19 to 68) of the original bone length. The mean healing index was 34.7 days/cm (18.2 to 117). A healing index of > 50 days/cm was observed in eight bones (11%).

There were 11 early fractures (three femoral and eight tibial) (16%) in eight patients (Table II). All but one fracture occurred without significant trauma. There were six type 1 fractures and five type 2 fractures. A total of six occurred while the pins were *in situ* and five of these were treated successfully with further fixation using the frame. The other patient sustained an open tibial fracture in a fall and was treated with irrigation and re-application of the frame.

The fractures that appeared while the pins were *in situ* occurred within four days of removal of the frame, and five occurred after removal of the pins. The mean delay between removal of the pins and the fracture was 3.6 days (1 to 7). All were minimally displaced and conservatively treated with traction or a cast.

The shape of the callus was cylindrical in four fractures, concave in two, lateral in three, and central in two. All early fractures healed without loss of the length gained or the development of permanent deformity.

Late fracture was observed in six tibiae (Table III). The mean time between removal of the frame and fracture was 18.3 weeks (3.3 to 38.4) There were five type 1 and one type 2 fractures and three had a healing index of > 50 days/cm. The shape of the callus was lateral in three and cylindrical, concave and central in one each, respectively. A total of four of the fractures were associated with unexpected excessive loading on the affected limb during daily or sporting activities. All were minimally displaced and successfully treated with a cast or a brace. The remaining two patients had an undisplaced stress fracture within the sclerotic regenerate. Reduction of the stress at the fracture site by walking on crutches lead to union.

The shape of the callus was the only variable associated with the occurrence of early fracture in univariate (p = 0.001) and multivariate (p = 0.005) analyses (Tables IV and V). The rate of early fracture was six in 60 limbs (10%) in fusiform, cylindrical, or concave shaped callus, and five in ten limbs (50%) in either lateral or central shaped callus. The estimated OR of early fracture was nine times higher in the limbs with the latter pattern of callus than in those in the former group (OR 9.00, 95% CI 2.01 to 40.3). Tibial lengthening, healing index and the shape of the callus were related to the occurrence of late fracture in univariate analysis (p = 0.049, p = 0.002 and < 0.001, respectively). The rate of late fracture was much higher in the bones with a healing index of ≥ 50 days/cm (3/8 bones, 38%) than in those with a healing index of < 50 days/cm (3/62 bones, 5%). Multivariate logistic regression analysis demonstrated that the shape of the callus was the strongest predictor for late fracture (p = 0.002). A callus with a lateral or central shape had a much higher risk of late fracture than other shapes (OR 19.3, 95% CI 2.91 to 128).

Table IV. Univariate predictive factors for early and late fractures. Continuous variables are expressed as the mean with standard deviation (SD)

	Presence of an early fracture (n = 11)	Absence of an early fracture) (n = 59)	p-value	Presence of a late fracture (n = 6)	Absence of a late fracture (n = 64)	p-value
Gender (male/female)	7/4	23/36	0.129	3/3	27/37	0.712
Age (yrs)	13.9 (SD 3.5)	14.7 (SD 4.10	0.55	14.0 (SD 2.1)	14.7 (SD4.3)	0.817
Bone (femur/tibia)	3/8	23/36	0.461	0/6	26/38	0.049*
BMI (normal/high)	7/4	41/18	0.701	3/3	45/19	0.305
Amount of lengthening (cm)	9.3 (SD 1.2)	9.2 (SD 1.3)	0.554	9.8 (SD 1.3)	9.2 (SD 1.3)	0.448
Amount of lengthening (%)	47.0 (SD 13.3)	44.3 (SD 13.3)	0.429	50.3 (SD 8.9)	44.2 (SD 13.5)	0.24
Healing index (< 50/≥ 50)	8/3	54/5	0.072	3/3	59/5	0.002*
Callus shape (F/Cy/Co/ L/Ce)	0/4/2/3/2	7/29/18/5/0	0.001*	0/1/1/3/1	7/32/19/5/1	< 0.001*

BMI, body mass index; F, fusiform; Cy, cylindrical; Co, concave; L, lateral; Ce, central
*statistically significant

Table V. Multivariate logistic regression analysis for early and late fractures

Early fracture	p-value	Odds ratio	95% CI
Callus shape (F, Cy, Co *vs* L, Ce)	0.005	9.00	2.01 to 40.3
CI, confidence interval; F, fusiform; Cy, cylindrical; Co, concave; L, lateral; Ce, central			
Late fracture	**p-value**	**Odds ratio**	**95% CI**
Callus shape (F, Cy, Co *vs* L, Ce)	0.002	19.3	2.91 to128

CI, confidence interval; F, fusiform; Cy, cylindrical; Co, concave; L, lateral; Ce, central

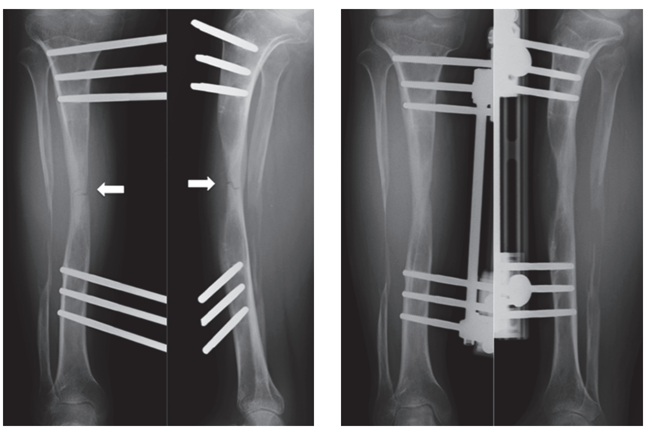

Fig. 1a Fig. 1b

Radiographs of the right tibia in a 16-year-old male with achondroplasia with the pins *in-situ* showing a) a minimally displaced tibial fracture (arrow) at the narrowest part of the regenerate. Following minor trauma, this fracture occurred three days after removal of the frame. Figure 2b - the fracture was successfully treated with re-application of the frame for four weeks.

Discussion

Fracture after extensive limb lengthening in patients with ACH or HCH is still a major complication. Several techniques including CT scan, ultrasound, dual energy X-ray absorptiometry (DEXA), and Orthometry, have been used to evaluate the regenerate and determine when the external fixator should be removed.[14-19] Plain radiographs are, however, usually used to decide when the external fixation should be removed as this is simple and inexpensive. The incidence of early fracture (16%) in our series suggested difficulty in determining the timing of removal of the fixation by radiological appearances alone. Specific criteria for removal of the fixation should be firmly established to prevent fracture of the regenerate.

For fractures which occurred while the pins remained *in situ*, re-application of the frame restored alignment and uneventful healing without additional procedures (Fig. 1). All of these fractures occurred within four days of removal of the frame. Fractures after the subsequent removal of the pins were also observed within a week in all patients. Forriol et al[20] reported in a series studying the radiographs of 55 patients, that fracture occurred in the first two weeks after removal of the fixator in 88% of cases. We thus recommend a period of observation of a few weeks with the pins *in situ* before their final removal.

Bone regenerates are loaded not only in compression but also with bending and torsional stresses after removal of the fixator.[21,22] Since the latter stresses are not encountered during dynamisation, unexpected bending or torsional loads may cause an early fracture. The use of short-term immobilisation by casts or braces after the final removal of the pins could prevent excessive bending or torsional loads.

During a review of 34 lower limb lengthening procedures in patients with ACH and associated conditions, Launay et al[23] reported that the rate of fracture was higher in those aged < nine years. However, we did not find any association between the age of the patient and occurrence of fracture. This may be due to the relative older patients in our series. Simpson and Kenwright[11] reported considerable variation in the location of the 17 fractures that occurred within the regenerate in six, at the bone/regenerate junction in six, and at distant sites in five. In contrast, in our series, most of the early fractures (six, 5%) occurred within the regenerate and there were no fractures at distant sites. Excessive lengthening was occasionally associated with decreased new bone formation in the middle of the regenerate. Venkatesh et al[9] demonstrated that half of the femora in patients with ACH which are lengthened by > 50% of their initial length tended to have a thin or concave shaped callus, some of

Fig. 2

Lateral radiograph of the right tibia in a 16-year-old female with achondroplasia showing an undisplaced stress fracture of the tibia (arrow) within the hard callus. In the absence of trauma, this fracture was noticed 13.1 weeks after the screws had been removed.

which resulted in fracture. In agreement with their findings, we also observed that most fractures of the regenerate were associated with lateral or central shaped callus. When thin callus is recognised during distraction, attempts should be made to improve the shape of the callus by changing the rhythm of distraction, such as slowing down the rate of distraction, or halting distraction and subsequent compression.[9] Some additional measures to stimulate bone formation should be considered, such as low-intensity pulsed ultrasound or the use of bisphosphonates, osteogenic cytokines or growth factors.[24-27]

There have been few reports describing late fractures after limb lengthening. Faber et al[28] reported seven late fractures in 46 lengthenings, three femoral and four tibial, including one spontaneous fracture in 23 patients. Simpson and Kenwright[11] reported three insidious late fractures with deformities, out of 17 fractures in 180 lengthened segments. These papers, however, lacked a detailed description of the predisposing factors and pattern of late fractures. We clearly demonstrated that bone with a larger healing index and with lateral or central thin callus had a greater risk of late fracture. Delay in consolidation and maturation of the distraction callus leads to prolonged remodelling and insufficient strength of the regenerate. Indeed, in our series, most late fractures occurred in sclerotic regenerates (hard callus) where the medullary cavity was poorly formed (Fig. 2). The excessive loading of vulnerable hard callus should be avoided. For the limbs with thin callus and a larger healing index, careful management will be needed during the formation of the medullary cavity throughout the regenerate, as confirmed on radiographs.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by G. Scott and first proof edited by J. Scott.

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