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Evaluating the Effectiveness of Prophylactic Intramedullary Rodding on Fracture Prevention after Femoral Lengthening in Achondroplasia

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Als meus pares, pel seu infinit suport incondicional.

Evaluating the Effectiveness of Prophylactic Intramedullary Rodding on Fracture Prevention after Femoral Lengthening in Achondroplasia

ABSTRACT

Introduction:

Extensive limb lengthening (ELL) is effective for correcting growth deficit in patients with short stature dysplasia, however, it is associated with complications such as bone fracture. This study aimed to evaluate the effectiveness of prophylactic intramedullary Rush rodding in preventing femoral refractures in achondroplasia patients undergoing lengthening treatment.

Methods:

This is a retrospective study that included 30 patients with genetically diagnosed achondroplasia who underwent bilateral femoral lengthening. Cohort A (14 patients, 28 femurs) did not receive Rush rodding, while cohort B (16 patients, 32 femurs) received prophylactic intramedullary Rush rodding.

Results:

Cohort A had a mean age at external fixation surgery of 14,7 ± 1,5 years, while cohort B had 14,2 ± 1,7 years. Mean femoral lengthening was 13,9 ± 2,3 cm in cohort A and 14,4 ± 3,3 cm in cohort B. Median duration of treatment with Rush rodding was 505,5 days (203 - 820 days).

Significant differences were observed between the cohorts in the occurrence of fractures and refracture major complications. Cohort A had five fractures (17,9%), resulting in femoral shortening > 1 cm and requiring surgical intervention. Cohort B had one fracture (3,1%), attributed to premature weight-bearing. The p-value for fractures between cohorts was 0,088 (0,021 excluding premature weight-bearing fracture). Cohort B had a significantly lower incidence of refracture major complications (p-value 0,018), managed conservatively without surgical intervention.

Conclusions:

Prophylactic intramedullary Rush nailing effectively reduces refractures and the need for surgical intervention in achondroplasia patients undergoing limb lengthening, playing a crucial role in improving outcomes and minimizing complications.

Avaluació de l'efectivitat de la ferulització intramedular profilàctica en la prevenció de fractures després de l'allargament femoral en l'acondroplàsia

RESUM

Introducció:

L'allargament extensiu de les extremitats (ELL) és efectiu per corregir el dèficit de creixement en pacients amb displàsia de baixa estatura, però està associat amb complicacions com la fractura òssia. L'objectiu d'aquest estudi era avaluar l'efectivitat de la fixació profilàctica amb clau Rush en la prevenció de refractures femorals en pacients amb acondroplàsia sotmesos a allargament.

Mètodes:

Aquest és un estudi retrospectiu amb 30 pacients amb acondroplàsia diagnosticada genèticament sotmesos a allargament bilateral de fèmur. La cohort A (14 pacients, 28 fèmurs) no va rebre fixació amb clau Rush, i la cohort B (16 pacients, 32 fèmurs) que va rebre fixació intramedular profilàctica amb clau Rush.

Resultats:

La cohort A va presentar una edat mitjana en la cirurgia de fixació externa de 14,7 ± 1,5 anys i un allargament femoral mitjà de 13,9 ± 2,3 cm. Per altra banda, la cohort B va presentar una edat mitjana de 14,2 ± 1,7 anys i allargament femoral mitjà de 14,4 ± 3,3 cm. La durada mitjana del tractament amb clau Rush va ser de 505,5 dies (rang 203 - 820 dies).

S'observen diferències significatives entre les cohortes en la incidència de fractures i complicacions majors de refractura. En la cohort A, cinc fractures (17,9%) amb acorçament femoral > 1 cm i requerint intervenció quirúrgica. En la cohort B, una fractura (3,1%) atribuïda a càrrega prematura. El valor p per a les fractures entre les cohortes és de 0,088 (0,021 excluint la fractura per càrrega prematura). La cohort B presenta una incidència significativament menor de complicacions majors de refractura (valor p de 0,018) gestionades de manera conservadora.

Conclusions:

La fixació profilàctica amb clau Rush redueix de manera efectiva les refractures i la necessitat d'intervenció quirúrgica en pacients amb acondroplàsia sotmesos a allargament, millorant els resultats i minimitzant les complicacions.

Evaluación de la efectividad de la ferulización intramedular profiláctica en la prevención de fracturas después del alargamiento femoral en la acondroplasia

RESUMEN

Introducción:

El alargamiento extensivo de extremidades (ELL, por sus siglas en inglés) es efectivo para corregir el déficit de crecimiento en pacientes con displasia de baja estatura, sin embargo, está asociado con complicaciones como fracturas óseas. El objetivo del estudio fue evaluar la efectividad de la fijación profiláctica con clavo Rush en la prevención de refracturas femorales en pacientes acondroplásicos después del alargamiento.

Métodos:

Este es un estudio retrospectivo con 30 pacientes diagnosticados genéticamente con acondroplasia sometidos a alargamiento bilateral de fémur. La cohorte A (14 pacientes, 28 fémures) no recibió fijación con clavo Rush, y la cohorte B (16 pacientes, 32 fémures) recibió fijación intramedular profiláctica con clavo Rush.

Resultados:

La cohorte A presentó una edad promedio en la cirugía de fijación externa de 14,7 ± 1,5 años y un alargamiento femoral promedio de 13,9 ± 2,3 cm. Por otro lado, la cohorte B presentó una edad promedio de 14,2 ± 1,7 años y un alargamiento femoral promedio de 14,4 ± 3,3 cm. La duración promedio del tratamiento con clavo Rush fue de 505,5 días (rango 203 - 820 días).

Se observan diferencias significativas entre las cohortes en la incidencia de fracturas y complicaciones mayores de refractura. En la cohorte A, cinco fracturas (17,9%) con acortamiento femoral > 1 cm y que requirieron intervención quirúrgica. En la cohorte B, una fractura (3,1%) atribuida a carga prematura. El valor p para las fracturas entre las cohortes es de 0,088 (0,021 excluyendo la fractura por carga prematura). La cohorte B presenta una incidencia significativamente menor de complicaciones mayores de refractura (valor p de 0,018) gestionadas de manera conservadora.

Conclusiones:

La fijación profiláctica con clavo Rush reduce de manera efectiva las refracturas y la necesidad de intervención quirúrgica en pacientes con acondroplasia sometidos a alargamiento, mejorando los resultados y minimizando las complicaciones.

Evaluating the Effectiveness of Prophylactic Intramedullary Rodding on Fracture Prevention after Femoral Lengthening in Achondroplasia

Introduction

Background and Context

Achondroplasia is the most common short stature skeletal dysplasia. Incidence consists of 1 in every 25,000-30,000 individuals, leading to a prevalence of 250,000 worldwide [4].

Achondroplasia has an autosomal dominant inheritance, with fully penetrant mutations [4]. There is a direct relationship between achondroplasia and mutations in FGFR3 (Fibroblast Growth Factor Receptor 3) gene on chromosome 4p16.3. Furthermore, mutations in the FGFR3 protein come from the same nucleotide pair and always result in a glycine to arginine substitution (Gly380Arg) [5]. Achondroplasia is a metaphyseal dysplasia [4]. Mutations in FGFR3 have demonstrated an increased signaling that stabilizes the receptor, enhances dimerization as well as tyrosine kinase activity. Paradoxically, it was found that an increase in FGFR3 signaling severely suppresses the mechanisms of proliferation and maturation of growth plate chondrocytes, which results in a decreased size of the growth plate, decreased bone elongation and reduced volume of the trabecular bone. Therapeutic approaches, such as Vosoritide (C-Type Natriuretic Peptide Analog) with recent succeeding results in phase III clinical trials [6], are being evaluated to improve endochondral bone growth in patients with mutations in the FGFR3 protein [5].

Most commonly, achondroplasia is diagnosed in early infancy, although there has been an increase in prenatal diagnosis throughout the years. Many complications can only be prevented if detected in early childhood, meaning that early diagnosis is beneficial and essential. There are yet no published diagnostic criteria, nevertheless, clinical and radiologic characteristics allow a good diagnostic approach to this type of dysplasia (refer to Table 1). Please note that not all infants will display every characteristic [4].

Table 1. Clinical and Radiological features in Achondroplasia that help with diagnosis orientation (adapted from Pauli R. M. (2019) 4-6) [4]

Clinical	Radiological
Small stature (not constant in all infants)	Short and robust tubular bones
Short limbs and rhizomelic (proximal) shortening	Squared-off iliac wings
Macrocephaly (anterior fontanel can be large and persist until the age of 5-6 years)	Flat and horizontal acetabula
Midface flattening and flat nasal bridge due to underdeveloped cartilaginous bones)	Narrowing of the sacrosciatic notch
Small chest and overly compliant ribs (may result in paradoxical movement at inspiration)	Proximal femoral radiolucency
Thoracolumbar kyphosis (developed within infancy, not present at birth)	Narrowing of the interpediculate distance of the caudal spine
Lumbar hyperlordosis ("swayback" walk)	Short proximal and middle phalanges
Limited elbow extension (elbows become progressively stiffer with age)	Narrowing of the foramen magnum [5]
Short fingers and trident hands (excess separation between third and fourth fingers)	These characteristics can be seen on an anteroposterior radiograph of the femurs and pelvis.
Hypermobile hips and knees	
Bowing of the mesial segment of the legs	
Hypotonia and joint hypermobility ("floppy" infants)	

Published Evidence on Surgical Femoral Elongation

To date, the most effective treatment for growth deficit in patients with achondroplasia is surgical distraction osteogenesis [1]. Professor Ilizarov described distraction osteogenesis in the 1950s. The technique is based on the principle of bone regeneration and it is still used today for limb lengthening, as well as correction of nonunions and limb deformities [7]. This surgical procedure consists of performing an osteotomy, followed by implantation of an external fixator. Then, for several months (usually close to a year) the external fixator is gradually modified to begin lengthening, 1mm per day as a standard.

Nowadays, there are several different types of external fixators available for bone elongation (monolateral, bilateral, sector, semi-circular, circular, and combined). There is a preference regarding the use of rod monolateral external fixators due to their smaller size and weight, which reduces pain, prevents infections and diminishes the risk of neurovascular damage, compared to the external circular multi-axis system. On the other hand, Intramedullary Limb Lengthening methods (such as PRECICE) have been developed. These consist of a long intramedullary rod which can be elongated using a magnet system. Even though this system drastically reduces the pain and inflammation around transosseous elements (compared to external fixator systems), intramedullary rods are produced using very expensive titanium alloys. Furthermore, internal fixators need a minimum bone diameter (PRECICE, for example) which cannot be used on upper limbs. Finally, combined methods such as LON (Lengthening Over Nail) and LATN (Lengthening and Then Nailing) consist of removing the external fixator after the distraction period and then using an internal fixator for the consolidation period. This reduces significantly the time the patient wears the external fixator [3].

Considerable controversy persists regarding the optimal and safest technique for limb lengthening. The conventional Ilizarov's method has several disadvantages, such as higher EFT (external fixation time) and an increased risk of refracture after frame removal. Moreover, this technique is associated with a high incidence of other complications, such as pin-site infections, joint stiffness and muscle contracture [7]. Finally, excessive time with external fixation may have negative psychological consequences on the patient, increasing frustration and decreasing compliance [8]. However, the LATN (Lengthening and Then Nailing) method, which is also the one employed in this study, has been associated with multiple complications, including severe pin-site infection and nail breakage [7].

It has been challenging to assess complications related to the previously mentioned techniques because achondroplasia is a rare disease and ELL treatment is the patient's choice. As a result, most studies suffer from limited sample sizes and related complications to lengthening procedures have a low incidence.

Objectives

Femoral fracture is a common complication after femoral lengthening [1,2,9]. The purpose of this study is to determine whether prophylactic intramedullary Rush rodding is an effective method to prevent femoral refracture after extensive limb lengthening (ELL) in patients genetically diagnosed with achondroplasia.

The null hypothesis of this study assumes that there are no statistically significant differences in the effectiveness of prophylactic intramedullary Rush rodding in preventing femoral refractures and reducing associated complications, in comparison with the group that does not use Rush rodding after lengthening treatment ($H_0 \equiv p_{noRush} = p_{Rush}$).

Materials and Methods

Study Design

This retrospective study included 30 patients with genetically diagnosed achondroplasia who underwent bilateral femoral lengthening procedures. The study was conducted at the Bone Reconstruction and Lengthening Unit, Quirón Dexeus University Hospital, Barcelona, with surgical procedures performed between 2006 to 2020 and follow-up until December 2022.

Inclusion criteria comprised patients with achondroplasia who underwent bilateral femoral lengthening using a monolateral external fixator. Patients who underwent lengthening procedures with combined techniques or self-expanding intramedullary nails due to limb length discrepancy were excluded. Patients with other types of limb discrepancies and dysplasias, such as congenital limb defect or hypoachondroplasia, were also excluded from the study.

Consequently, the study involved the comparison of two cohort groups. Cohort A consisted of 14 patients (with 28 femoral lengthenings) without prophylactic intramedullary Rush rodding, while Cohort B included 16 patients (with 32 femoral lengthenings) with prophylactic intramedullary Rush rodding following ELL.

Ethical Considerations and Sample Size

The study obtained institutional ethical approval from the COMITÉ ÉTICO DE INVESTIGACIÓN con Medicamentos (CEIm) GRUPO HOSPITALARIO QUIRÓNSALUD-CATALUNYA, located at c/ Pedro i Pons 1, 08195 Sant Cugat del Vallès (Barcelona), on April 18, 2023 (acta nº 09/2023). Furthermore, the study adhered to the principles outlined in the Declaration of Helsinki for ethical research involving human participants.

Patients who participated in this study were under the age of 18, therefore, informed consent for undergoing limb lengthening procedures was obtained from their respective legal guardians. All data collected from patients was anonymized to ensure confidentiality and protect their privacy.

The sample size of 30 patients in this study can be justified by the rarity of achondroplasia, with a worldwide prevalence of 250,000 individuals. Given that extensive limb lengthening is not a mandatory or essential treatment for all patients and is chosen based on individual preferences, the number of surgeries performed is limited. Additionally, the inclusion of patients treated by the same surgical department (Bone Reconstruction and Lengthening Unit at ICATME, Institut Català de Traumatologia i Medicina de l'Esport, Quirónsalud-Catalunya Hospital Group), ensures consistency in the procedures. It should be noted that although the sample size is 30 patients, the evaluation will involve a total of 60 femoral lengthenings due to the bilateral nature of the procedure.

Surgical Technique

The surgical technique involved the following steps. Firstly, osteotomies were performed at the medial-proximal level using a perimetric brocade. Subsequently, distraction osteogenesis was employed in all patients to achieve limb elongation, utilizing a monolateral external fixator. The specific external fixator used was a 6mm red Triax without hydrox, chosen for its stability and support during the lengthening process. A latency period of 7 days following femoral osteotomy and external fixation surgery was implemented before the initiation of the lengthening process. Lengthening rate was 1 mm per day (0,5 mm every 12 hours). For cohort B patients, distraction was continued until desired length was achieved and the external fixator was not removed until at least 3 out of the 4 cortices viewed on the anteroposterior and lateral radiographs had begun corticalization. Thereafter, surgery to remove external fixation was performed and a prophylactic intramedullary Rush nail was implanted. On the other hand, in cohort A, external fixation was only removed when complete corticalization was achieved. Consequently, cohort A had a longer duration with external fixation. Please refer to figures 6 to 10 for an overview of the ELL process posteriorly using prophylactic intramedullary Rush nailing in cohort B.

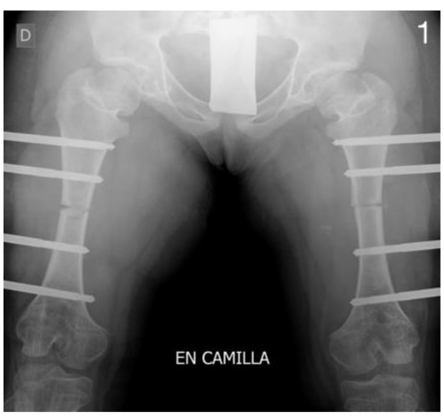
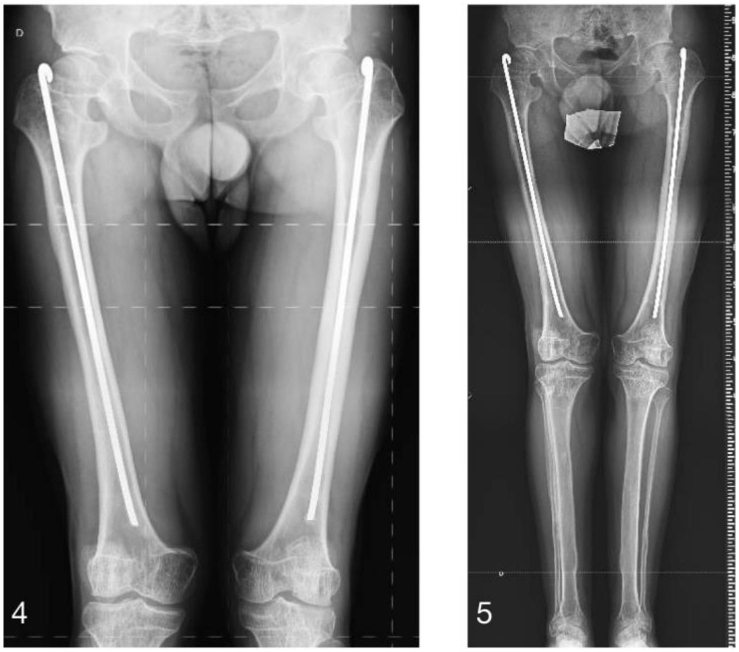


Figure 1. *Radiograph after osteotomy surgery with implantation of external fixator. Procedure is performed bilaterally, so on both femora.* ***Figure 2****. Follow-up at 8 cm lengthening. Notice ossification callus formation.* ***Figure 3****. Follow-up at 15 cm lengthening. Ossification callus with increased density.*



Figures 4 and 5. *Placement of Rush rods at the completion of femoral elongation and progression until corticalization and medullary reaming.*

Patient Characteristics, Data Collection and Study Variables

All patients participating in the study were genetically diagnosed with an achondroplasia type of dysplasia. All lengthenings were performed bilaterally, so data was collected for both right and left femora, accordingly. Demographic information, including the patients' hospital of origin, sex, date of birth, age, date of last follow-up, etiology, and type of dysplasia, was recorded for each participant. Preoperatively and postoperatively, various measurements were taken using calibrated tellemetries, including length (in millimeters), mechanical axis deviation (DAM), and mechanical lateral distal femoral angle (mLDFA). Moreover, date of the external fixation surgical procedure, age at the start of external fixation, type of external fixation, level and type of osteotomy, date of external fixation removal, indication for posterior intramedullary Rush rodding, and type of callus formation for both femurs were recorded.

Lastly, the following complications related to the procedure, if present, were documented:
The primary variable of interest was the number of refractures following femoral lengthening. Additionally, the secondary variable examined was the deviation of the femoral axis. Other outcome measures assessed included premature consolidation, joint luxation, muscle contracture, pin-site infection, neurological injury, vascular injury, axial deviation, joint stiffness, and delayed consolidation.

Statistical Analysis

The data analysis was performed using the SPSS statistical software package version 29 (IBM Corp., Armonk, NY, USA). Continuous variables, such as radiographic calculations related to femoral lengths and axis deviation characteristics, were assessed using the t-student test and one way Anova. Mean and standard deviation were used to represent variables that followed a normal distribution, while variables that didn't follow a normal distribution were presented as median with a range. Categorical variables, including variables of interest and complications, were analyzed using Fisher's exact test due to the small sample size (N < 5). Fisher's exact test allowed to examine associations and significance in 2x2 tables. If sample size of categorical variables was larger (N > 5), a chi-squared test was performed. The recorded p-values for all results were two-sided. These statistical methods enabled valid comparisons and interpretations of outcomes related to femoral lengthening and Rush rodding procedures.

Results

Table 2 shows patients' demographic characteristics and measures collected using calibrated telemetries of before and after lengthening data. In cohort A, the mean age at the time of external fixation surgery was 14,7 ± 1,5 years, while in cohort B, it was 14,2 ± 1,7 years (p-value 0,375). The external fixation time (EFT) was 329,1 ± 62,0 days in cohort A and 301,5 ± 39,9 days in cohort B (p-value 0,152), which equals to a total of 11 and 10 months of EFT, respectively. The mean femoral lengthening was 13,9 ± 2,3 cm in cohort A and 14,4 ± 3,3 cm in cohort B (p-value 0,580). The external fixation index (EFI; days/cm) was 24,7 ± 7,7 in cohort A and 22,2 ± 7,2 in cohort B (p-value 0,369). There were no significant gender differences between the groups (p-value 0,730). The median duration of treatment with prophylactic Rush rodding was 505,5 days (203 - 820 days). Noticeably, there are statistically significant differences between groups regarding length of the right and left femur before external fixation surgery, 0,016 and 0,009. Statistically significant differences are also observed between groups regarding length of the right and left femur posterior to external fixation surgery, 0,009 and 0,002 respectively. For the rest of annotated variables, Table 2 demonstrates no statistical differences between group A (no Rush nailing) and group B (with Rush nailing) regarding MAD and mLDFA before and after lengthening, as well as gained length, MAD difference after lengthening and External Fixation Index (EFI).

Please refer to Appendices 1 and 2 for an overview of the progression of two case examples of patients diagnosed with achondroplasia. Appendix 1 illustrates the case of a patient who underwent ELL without subsequent Rush nailing, while Appendix 2 presents the case of a patient who underwent ELL with Rush nails implanted afterwards.

Table 2. Patient Demographics with Radiographic Data before and after Femoral Lengthening

	Group A – Without Rush Nailing (n = 14)	Group B – With Rush Nailing (n = 16)	p-value
Demographic data			
Gender (male)	6 (42,9)	8 (50,0)	0,730
Age at external fixation surgery (years)	14,7 ± 1,5	14,2 ± 1,7	0,375
Preoperative Radiographic Results			
Length of Right Femur (cm)	23,5 ± 1,6	26,4 ± 3,9	**0,016***
Length of Left Femur (cm)	23,2 ± 1,8	26,3 ± 3,8	**0,009***
MAD† of Right Femur (mm)	- 3,2 ± 16,6	- 10,0 ± 17,4	0,280
MAD† of Left Femur (mm)	- 4,4 ± 17,9	- 0,2 ± 16,6	0,515
mLDFA‡ of Right Femur (º)	88,3 ± 5,8	90,3 ± 4,7	0,600
mLDFA‡ of Left Femur (º)	88,4 ± 7,05	89,1 ± 4,6	0,757
Postoperative Radiographic Results			
Length of Right Femur (cm)	37,2 ± 2,7	40,4 ± 3,5	**0,009***
Length of Left Femur (cm)	37,0 ± 2,7	41,1 ± 3,6	**0,002***
MAD† of Right Femur (mm)	- 0,2 ± 16,0	- 8,4 ± 20,8	0,243
MAD† of Left Femur (mm)	- 3,5 ± 12,9	- 2,8 ± 17,0	0,903
mLDFA‡ of Right Femur (º)	90,2 ± 4,9	89,6 ± 5,5	0,755
mLDFA‡ of Left Femur (º)	91,8 ± 7,8	90,4 ± 6,0	0,587
Lengthening Radiographic Results			
Lengthening of Right Femur (cm)	13,8 ± 2,3	14,1 ± 3,2	0,743
Lengthening of Left Femur (cm)	13,9 ± 2,4	14,7 ± 3,5	0,460
Mean** Femoral Lengthening (cm)	13,9 ± 2,3	14,4 ± 3,3	0,580
Mean** Femoral Lengthening (%)	59,8 ± 11,7	56,8 ± 17,8	0,595
MAD† difference on Right Femur (mm)	11,7 ± 10,4	9,7 ± 5,8	0,518
MAD† difference on Left Femur (mm)	11,1 ± 10,7	14,7 ± 10,8	0,375
EFT§ (days)	329,1 ± 62,0	301,5 ± 39,9	0,152
EFI# (days/cm)	24,7 ± 7,7	22,2 ± 7,2	0,369
Duration with Rush Nailing (days)	NA	505,5 (203 - 820)	NA

† Mechanical Axis Deviation (MAD): positive numbers indicate genu varum and negative numbers indicate genu valgum

‡ Mechanical Lateral Distal Femoral Angle (mLDFA)

§ External Fixation Time (EFT)

External Fixation Index (EFI) = number of days with external fixation divided by total lengthening (cm)

** Mean femoral lengthening for group A and B have an N = 28 and N = 32 respectively (mean of right and left femora). *Statistical significance achieved at p-value < 0,5

Variables are represented as mean ± SD, median (range) or absolute number (percentage)

NA: Not Applicable

For all continuous variables a t-student test was run, whereas a chi-squared test was used for categorical variables

The comparison of callus shapes in lengthened femora is illustrated in Graph 1 of Appendix 3. Without prophylactic intramedullary rodding, a majority (39%) of the femora exhibited a concave callus shape, as depicted in the pie chart. In contrast, femora treated with rush rodding demonstrated a higher incidence (56%) of cylindrical callus shapes (being the most optimal form). Group A had 9 (32%) fusiform callus shapes, while group B had 6 (19%), with a p-value of 0,232. In group A, there were 8 (29%) cylindrical callus shapes, whereas in group B, there were 18 (56%), indicating a statistically significant difference (p-value of 0,031). Lastly, group A exhibited 11 (39%) concave callus shapes, compared to 8 (25%) in group B, with a p-value of 0,235.

When comparing the total number of anomalous ossification callus between groups (combining fusiform and concave shapes), it is seen that in group A there are 20 (71%) out of 28 femora, while in group B there are 14 (44%) out of 32 femora (p-value of 0,031).

Please refere to Appendix 4 for further detail on callus types using Li's classification.

Table 3. Comparison of Complication Events Between Groups

	Group A - Without Rush Nail (n = 28) †	**Group B - With Rush Nail (n = 32)** †	**p-value**
Joint Luxation	0	0	NA
Neurological Injury	0	0	NA
Vascular Injury	0	0	NA
Joint Stiffness	0	0	NA
Delayed Consolidation	1 (3,6)	0	0,467
Premature Consolidation	1 (3,6)	1 (3,1)	1,000
Muscle Contracture	1 (3,6)	2 (6,3)	1,000
Refracture	5 (17,9)	1 (3,1)	0,088
Pin-site Infection	7 (25)	2 (6,3)	**0,043***
Axial Deviation	11 (39,3)	16 (50)	0,446
Total	26 (93)	22 (68,8)	**0,019***

† N in groups refers to the number of femurs with performed lengthening procedures (N = number of femurs

Variables are represented as absolute number (percentage)

NA: Not Applicable

Statistical differences between variables were analyzed using Exact Fisher's Test (p-value 2-sided exact significance) if N < 5 ; if N > 5, chi-squared test was used

*Statistical significance achieved at p < 0,05

On Table 3, incidence of several complications were recorded. To begin with, the majoriy of annotated complications had no statistically significant incidences between groups. There were no events regarding joint luxation, neurological injury, vascular injury and joint stiffness in any of the groups. One (3,6%) case of delayed consolidation occurred on group A and none on group B. There was one case per group regarding premature consolidation. There was one (3,6) muscle contracture case in group A and two (6,3) in group B. There were 5 refracture cases in group A (17,9%) and 1 in group B (3,1), with a p-value of 0,088. Last but not least, there were 11 cases of axial deviation (39,3%) in group A and 16 cases (50%) in group B, without statistically significant differences as well.

Nevertheless, there were statistical differences found regarding pin-site infection and total number of complication events. There were 7 (25%) pin-site infection cases in group A and 2 (6,3%) in group B, with a p-value of 0,043. Lastly, there were 26 (93%) total complication events out of 28 lengthened femurs in group A, and 22 (68,8) total complication events out of the 32 lengthened femurs in group B. The resulting p-value achieved statistical significance at 0,019.

As shown on table 4, Group A (without Rush nailing) had five refractures (17,9%) reported out of 28 femurs, all occurring within three weeks after the removal of the external fixator (early fractures). One fracture was located at a junctional place and four occurred in the regenerate callus. In Group B (with Rush nailing), there was one fracture (3,1%) in the regenerate callus, which was an early fracture as well. All fractures resulted in collapse, but the fracture with Rush nailing caused a loss of less than 1 cm of bone length and less than 5º angulation (considered a minor complication). In contrast, fractures without Rush nailing were considered major complications, resulting in a loss greater than 1 cm of bone length and collapsing into varus deformity with an angulation greater than 5º. Statistically significant differences were found regarding the appearance of refracture major complications between groups (p-value 0,018), showing zero events in group B (with Rush nailing) and 5 (17,9%) in group A (without nailing).

The callus shape for fractures in Group A was concave (type 3 of Li's classification), while the fracture in Group B had a cylindrical callus shape (type 2 of Li's classification). Callus density in Group A was type 7 (irregular) in one femur and type 6 (uniform) in the others. However, the fracture in Group B (with Rush nailing) had a type 2 (stripe) callus density, indicating incomplete consolidation of the femoral shaft. This indicates that the previously mentioned fracture was caused by premature weight-bearing (due to non-compliance of the patient).

Surgical intervention was required for all fractures without Rush nailing, what the author calls a setback (p-value 0,018). In contrast, the fracture with Rush nailing could be managed conservatively. This one resulted in a loss of 0,5 cm of length, which was successfully addressed using an 8 mm heel lift.

Table 4. Key Characteristics of the Refracture Complication Variable

	Group A - Without Rush Nailing (n = 28)	Group B - With Rush Nailing (n = 32)	p-value
Impact			
Minor Complication †	0	1 (3,1)	1,000
Major Complication ††	5 (17,9)	0	**0,018***
Callus			
Shape §			NA
Cylindrical (2)	0	1 (3,1)	
Concave (3)	5 (17,9)	0	
Density #			NA
Stripe (2)	0	1 (3,1)	
Uniform (6)	4 (14,3)	0	
Irregular (7)	1 (3,6)	0	
Time			
Early Fracture ‡	5 (17,9)	1 (3,1)	0,088
Late Fracture ‡‡	0	0	NA
Place			
Junctional	1 (3,6)	0	1,000
Regenerate Callus	4 (14,3)	1 (3,1)	0,175
Setbacks			
Collapse	5 (17,9)	1 (3,1)	0,088
Surgical Reintervention	5 (17,9)	0	**0,018***

† Minor complication: loss of less than 1 cm of length or less than 5º angulation
†† Major complication: loss greater than 1 cm of length or greater than 5º angulation

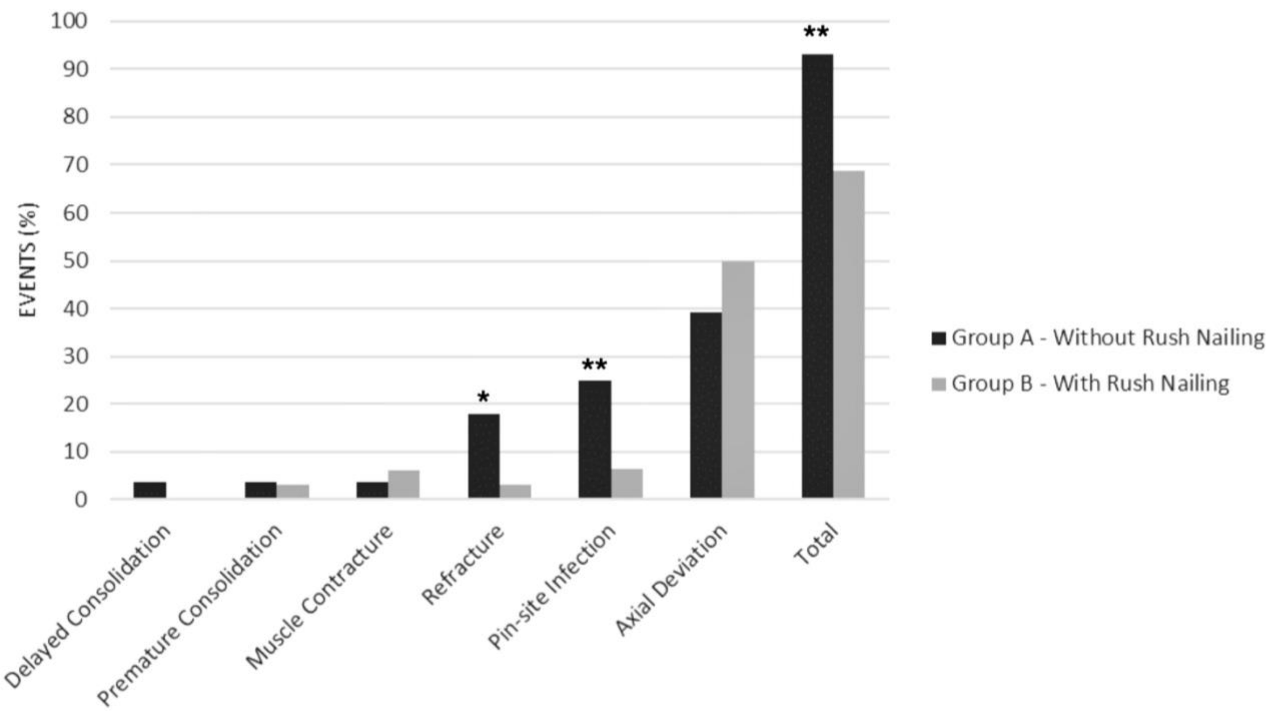
§ Shape of the callus: fusiform (1), cylindrical (2), concave (3), lateral (4), central (5).

Density characteristics of the callus: soft (1), stripe (2), speckle (3), adjacent (4), halftone (5), uniform (6), irregular (7), saw-tooth (8), solid (9), cyst defects (10)

‡ Early fracture: if occurrence before 3 weeks from removal of external fixator
‡‡ Late fracture: if occurrence after 3 weeks from removal of external fixator

Variables are represented as absolute number (percentage)
Statistical differences between variables were analyzed using Exact Fisher's Test (p-value 2-sided exact significance)
NA: Not Applicable
*Statistical significance considered when $p < 0,05$
N in groups refers to the number of femurs with performed lengthening procedures (N = number of femurs)

Graph 2. Complication Events Following Femoral Lengthening



** p-value ≥ 0,05 and ≤ 0,10 (valuable for clinical significance and close to statistical significance)*

*** p-value ≤ 0,05 (statistical significance is achieved)*

Graph 2 supports tables 3 and 4 illustrating the incidence of complications following femoral lengthening. The bar chart highlights statistically significant differences using 2 asterisks (p-value ≤ 0,05) regarding pin-site infections and total number of complications. One asterisk indicates a clinically significant value that approaches statistical significance (refracture events) with a p-value of 0,088. Although the refracture case in group B resulted from non-advised premature weight-bearing, it could be argued to exclude this patient from the study. If excluded, the p-value becomes 0,021 (5 fractures in group A out of 28 femurs, and 0 fractures in group B out of 30 femurs). However, the author chose not to exclude this patient due to the interesting nature of the case, and still consider a p-value of 0,088 to be clinically significant. Anyhow, a pattern can be clearly noticed, indicating that the group with rush nailing exhibits a significantly lower incidence of refracture complication cases.

Please refer to graph 3 in Appendix 5 for a visual representation regarding the impact of refracture complication cases.

Discussion

Overall, intramedullary prophylactic Rush nailing following femoral lengthening has been found to play a role in refracture events and to significantly reduce major complications related to refractures. This indicates that Rush nailing is a safe and a successfully optimal procedure after ELL in achondroplastic patients.

The radiographic measurements on table 2 regarding femoral lengths between the two groups reveal notable differences. Group B, which underwent extensive limb lengthening with Rush nailing, exhibited a statistically significant larger femoral length both before and after the procedure compared to Group A, which did not receive Rush nailing. Surprisingly, despite the longer femoral lengths in Group B, there were fewer fractures observed compared to Group A, which had shorter femurs without Rush nailing. The p-value for fractures between cohorts was 0,088 (very close to statistical significance) and a p-value of 0,021 (statistically significant) when excluding the patient who had a premature weight-bearing fracture. This suggests that increased femoral length in Group B did not correlate with a higher incidence of fractures and that rush nailing after limb lengthening succesfully prevents refracture events after procedure, even if treated femurs have greater length dimentions. It is worth mentioning that regarding clinically significant effectiveness of refracture prevention using Rush nailing (p-value 0,088) a statistically significant p-value could have probably been obtained with a larger sample size.

Regarding our primary variable, refracture of the femur, there were statistically significant differences in the occurrence of refracture major complications between the two groups (p-value 0,018). Group B, benefiting from Rush nailing, had zero refracture events with major complications, while Group A experienced five (17,9%) refractures with major complications. These findings highlight the crucial role of intramedullary Rush nailing in preventing major complications associated with femoral fractures, including a loss of femoral length greater than 1 cm or angulation exceeding 5º. Additionally, there were statistically significant differences (p-value 0,018) in the need for surgical reintervention after fractures, with all femurs in Group A requiring surgical treatment compared to none in Group B. The author considers this a setback, as it translates into more hospitalization time for the patient, longer recovery time and increased patient frustration due to longer duration of overall treatment. Consequently, it can confidently be asserted that intramedullary Rush nailing significantly reduces the necessity for surgical intervention following femoral fractures.

Furthermore, it is worth noting that the refracture case from Group B, resulting from premature weight-bearing, could have likely been prevented by adhering to postoperative instructions. Notably, this fracture, characterized by a callus density type 2 (indicating insufficient bone consolidation), was considered a minor complication and did not require surgical intervention. These findings demonstrate that intramedullary Rush nailing not only prevents fractures but also mitigates the occurrence of more severe complications. Even though patient from group B performed strictly unrecommended premature weight-bearing on the limbs (tried to walk), only one of both femurs was refractured. Also, surprisingly this was a minor complication refracture. Consequently, intramedullary rush nailing has been found to promote faster recovery, avoid the need of surgical reintervention, reduce patient trauma, and minimize healthcare costs. Moreover, Rush nailing prevented significant collapse in fracture from Group B, resulting in a 0,5 cm loss of length, whereas fractures in Group A led to a loss of length greater than 1 cm and varus deformities exceeding 5º.

It is also worth considering that all fractures in Group A exhibited concave callus deformity, which has a higher risk of fracture [9]. These findings may indicate that the use of an intramedular Rush nail following the removal of the external fixator could contribute to the preservation of proper callus formation, as corticalization is yet not terminated when the rush nail is inserted. Even though some studies suggest that early removal of the external fixator has been related to a higher risk of refracture [7], this was not found in this study. In fact, in this study, the opposite has been found when external fixation is removed at optimal time and Rush nailing is performed (LATN method). Notably, fractures did not occur in calluses that were not concave. A new hypothesis could arise relating external fixation removal at the beginning of corticalization (earlier than in Ilizarov's method) and then nailing, with better callus formation (achieving more cylindrical callus shapes). Further investigation into this relationship could provide valuable insights into fracture risk and guide future treatment approaches.

Moreover, incidence of other complication variables should be discussed. Previous studies have shown that LATN allows sufficient external fixation time to succesfully prevent axial deviation. However, this has not been seen in this study. Even though results were not statistically significant, there were more axial deviation cases in group B (50%) than in group A (39%). Nevertheless, the author suggests a relationship between longer femura with higher risk of axial deviation. Since femora with Rush nailing had greater statistically significant lengths than femora without nailing, this could have put femora from group B at a higher risk of developing axial deviation. There were two cases of muscle contacture in group B and only one in group A, which, even though it was not statistically significant, it was not expected. Literature supports that earlier removal of the external fixator with the LATN technique, allows patients to exercise the joint sooner and therefore lowering the risk of muscle contracture [7]. Regarding pin-site infection, there clear statistical significant results, demonstrating a lower risk in patients with rush nailing. This could be related to the earlier removal of the external fixator, which has more pin points than a rush nail (which only has one), thus playing an essential role in prevention of pin-site infection. Lastly, no higher risk regarding other observed complications was related to rush nailing as expected and suggested by previous studies [7].

This study had some limitations that should be acknowledged. Firstly, the sample size was relatively small, with only 30 patients and 60 femoral lengthenings included. However, it is important to note that since achondroplasia is a rare disease, this is a common problem that similar studies in the literature have faced when attempting to recruit large sample sizes. A good option could be to evaluate the same surgical procedure but in all types of dysplasia and limb discrepancies, not only in achondroplastic patients. However, this could create a bias as it is important to make studies on rare diseases only and specifically. Another option could be to collect all studies that have been done until today and create a meta-analysis.

Furthermore, complications associated with femoral lengthening have a low incidence, making it difficult to achieve statistically significant outcomes when comparing two different surgical procedures.

Last but not least, there is a bias to this study for being non blinded. Although it is also a common problem faced with these types of surgical procedures and small sample sizes among published literature [7] . However, it is important to note that observational studies tend to put authors into an overly optimistic view of the outcomes and thus inducing an observer bias.

Finally, the occurrence of a refracture case due to premature weight-bearing in group B, may have introduced a selection bias. Consequently, this could have altered the observed p-value of 0,088, which should in fact be 0,021 when excluding the patient.

Conclusions

In conclusion, our study highlights the effectiveness of prophylactic intramedullary Rush nailing in preventing fractures and reducing complications during femoral lengthening in Achondroplasia. The use of Rush nailing significantly reduced the incidence of refracture major complications and eliminated the need for surgical reintervention. Rush nailing, as well, significantly and successfully lowered the risk of pin-site infections. These findings support the adoption of Rush nailing as a valuable strategy for fracture prevention, promoting better patient outcomes and minimizing healthcare costs. Further research in this area will enhance treatment approaches and optimize patient care. Moreover, the impact of rush nailing using the LATN technique regarding callus formation could potentially be studied in the future.

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Availability of Data and Materials

Data supporting this study is available upon request to the corresponding author.

Conflict of Interest Statement

No competing interests were declared by the authors.

Gender Issues

The sample size of boys and girls was proportionally balanced, resulting in no significant gender differences within nor between cohorts.

References (NMA)

1. Legeai-Mallet, L., & Savarirayan, R. (2020). Novel therapeutic approaches for the treatment of achondroplasia. Bone, 141, 115579. [https://doi.org/10.1016/j.bone.2020.115579]
2. Dossanov, B., Trofimchuk, V., Lozovoy, V., Khmyzov, S., Dossanova, A., Zhukenov, O., Tuktiyeva, N., & Angelov, A. (2021). Evaluating the results of long tubular bone distraction with an advanced rod monolateral external fixator for achondroplasia. Scientific reports, 11(1), 14727. [https://doi.org/10.1038/s41598-021-94146-z]
3. Schiedel, F., Elsner, U., Gosheger, G., Vogt, B., Rödl, R. (2013). Prophylactic titanium elastic nailing (TEN) following femoral lengthening (Lengthening then rodding) with one or two nails reduces the risk for secondary interventions after regenerate fractures: a cohort study in monolateral vs. bilateral lengthening procedures. BMC Musculoskelet Disord, 14, 302. [https://doi.org/10.1186/1471-2474-14-302]
4. Pauli, R. M. (2019). Achondroplasia: a comprehensive clinical review. Orphanet Journal of Rare Diseases, 14(1), 1-28. [https://doi.org/10.1186/s13023-018-0972-6]
5. Ornitz, D. M., & Legeai-Mallet, L. (2017). Achondroplasia: Development, pathogenesis, and therapy. Developmental dynamics : an official publication of the American Association of Anatomists, 246(4), 291–309. [https://doi.org/10.1002/dvdy]
6. Wrobel, W., Pach, E., & Ben-Skowronek, I. (2021). Advantages and Disadvantages of Different Treatment Methods in Achondroplasia: A Review. International journal of molecular sciences, 22(11), 5573. [https://doi.org/10.3390/ijms22115573]
7. Xu, W. G. (2017). Comparison of intramedullary nail versus conventional Ilizarov method for lower limb lengthening: A systematic review and meta-analysis. Orthopedic Surgery, 9(2), 159-166. [https://doi.org/10.1111/os.12330]
8. Rozbruch, S. R., Kleinman, D., Fragomen, A. T., & Ilizarov, S. (2008). Limb lengthening and then insertion of an intramedullary nail: a case-matched comparison. Clinical Orthopaedics and Related Research, 466(12), 2923-2932. [https://doi.org/10.1007/s11999-008-0509-8]
9. Venkatesh KP, Modi HN, Devmurari K, Yoon JY, Anupama BR, Song HR. Femoral lengthening in achondroplasia: magnitude of lengthening in relation to patterns of callus, stiffness of adjacent joints and fracture. J Bone Joint Surg Br. 2009 Dec;91(12):1612-7. doi: 10.1302/0301-620X.91B12.22418. PMID: 19949126.

Appendices

Appendix 1. Case Example. Male achondroplastic patient with a prognosed adult size of 1,18 meters.

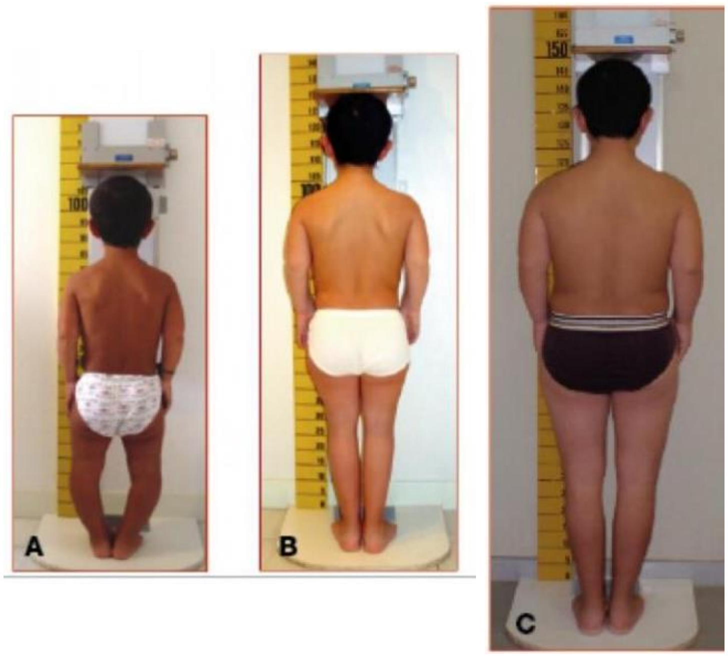


Figure 1A. *At 10 years old, initial size of 1,04m.*

Figure 1B. *At 12 years old, after bilateral 15 cm of lengthening on tibias.*

Figure 1C. *At 14 years old, after bilateral 15 cm of lengthening on femora. Final stature of 1,50m.*

Final height: 150 cm (30 cm of surgical lengthening + 16 cm of physiological growth).

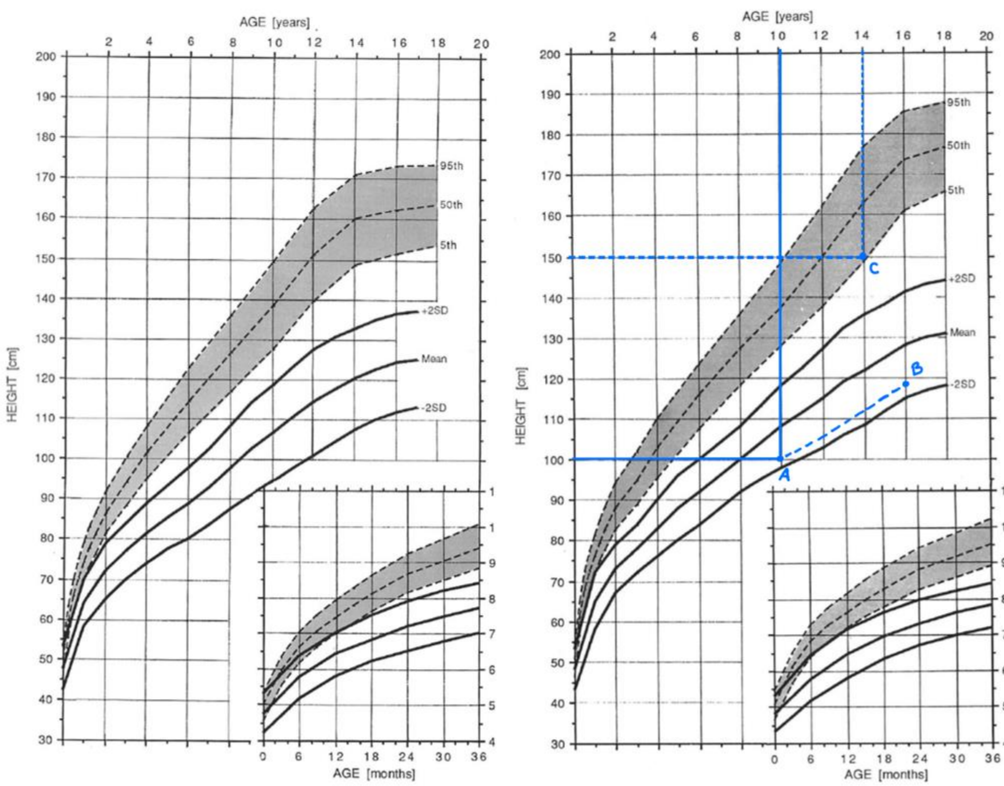


Figure 2. *Diagnostic linear height growth charts for achondroplastic females (on the left) and males (on the right). Curves for average statured individuals are shaded. Reproduced from Pauli R. M.(2019)15.)* [4]

In the male chart on figure 2, the author has illustrated the progression of the previously described case example using three points. Point A represents the patient's height at the age of 10. Point B indicates the predicted height of the patient after epiphyseal closure (or adult estimated stature). Point C represents the final height of the patient at the age of 14, after ELL and closed epipysis, which was 1.50 meters. As can be seen, this patient reaches the 5th percentile of height for the normal population of his age.

Appendix 2. Case Example. Figures 3 to 5 illustrate the progression of telemetries during the course of ELL for a female patient.

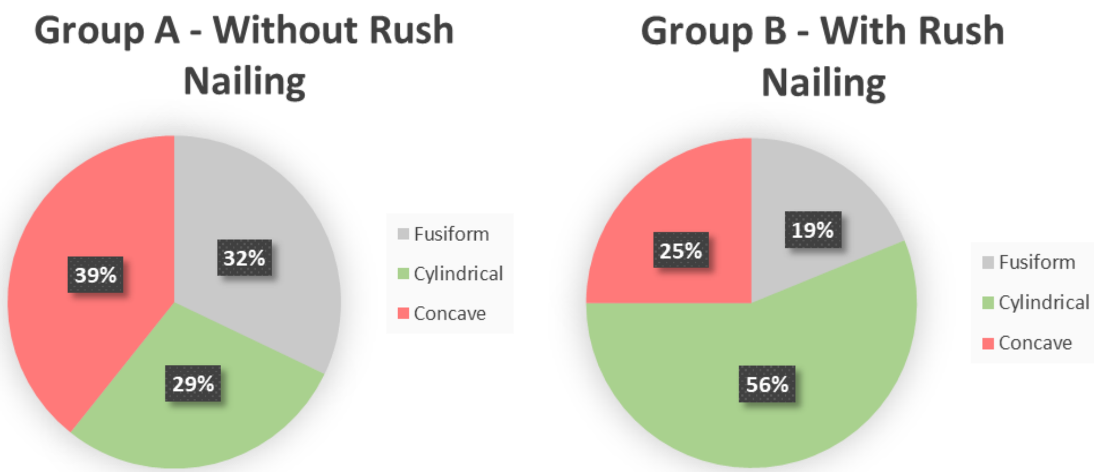
Figure 3. *Initial telemetry of patient previous to extensive limb lengthening (ELL)*

Figure 4. *Telemetry after 15 cm of lengthening on both tibias*

Figure 5. *End of ELL. Telemetry after 15 cm lengthening on tibias + 15 cm on femura*

Appendix 3.

Graph 1. Comparison of Callus Shapes in Lengthened Femora



Graph 1 evidences that patients who used rush nailing after frame removal developed a cylindrical and more optimal shape of the callus. This provides stability and therefore significantly prevents refracture of the femur after lengthening and removal of the external fixator.

Appendix 4. Li's Radiographic Classification of Callus Types

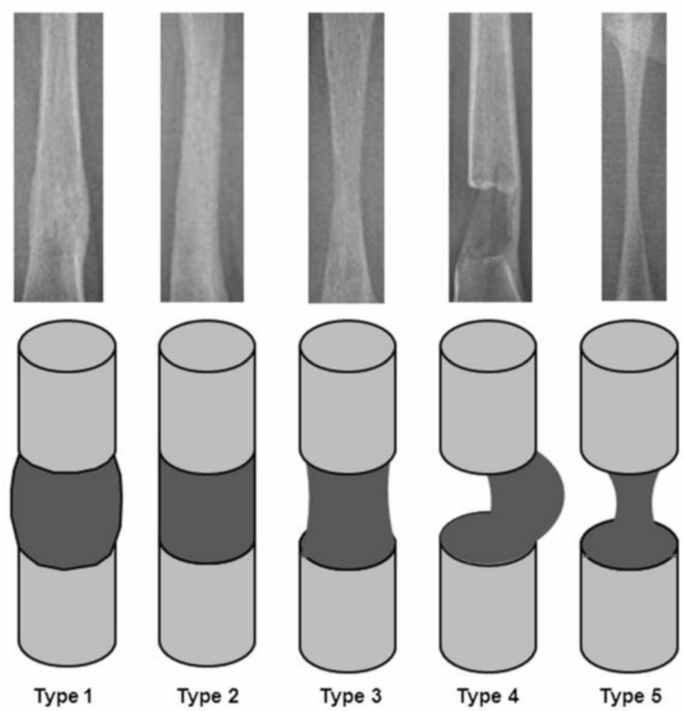
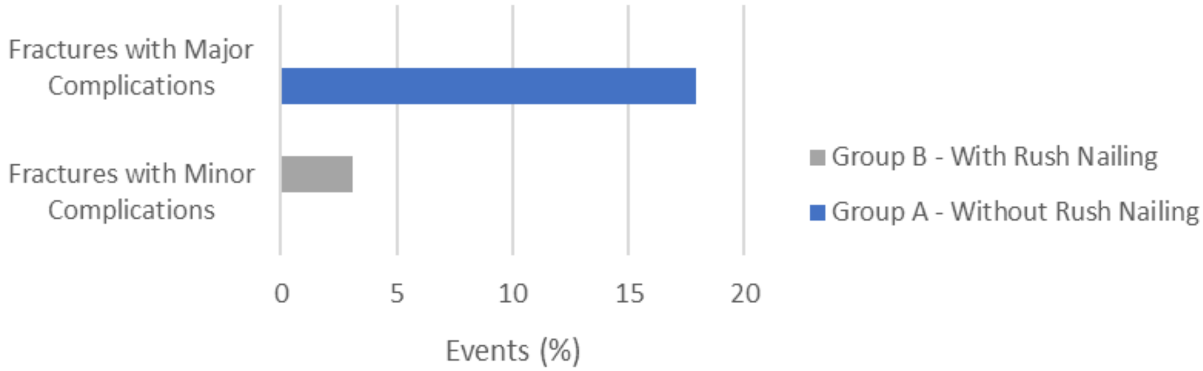


Figure 6 *(extracted from Schiedel F. (2013)3 [3]) . Radiographic appearance of the five types of callus shapes using Li's classification: fusiform (1), cylindrical (2), concave or hourglass (3), incomplete or only lateral (4), filiform or only central (5).*

Appendix 5.

Graph 3. Impact of Refracture Complication



Minor complication: loss of less than 1 cm of length or less than 5º angulation

Major complication: loss greater than 1 cm of length or greater than 5º angulation

Differences between groups result in statistical significance (p-value < 0,018)