Limb reconstruction with the Ilizarov method

Hubert Jan Oostenbroek

Dror Paley komt op bezoek bij Gavriil Ilizarov in Kurgan en ze beginnen in het Russisch te praten, vraagt een meegereisde Amerikaan: “Dror, why are you talking with the cook?”.

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Ledemaat reconstructie met de Ilizarov methode
(met Nederlandse samenvatting)

Proefschrift

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Chapter 1

Introduction

General introduction

When the Ilizarov method was introduced to the western world in the early nineteen eighties, it marked the beginning of a new way of thinking in limb reconstruction. In a short history, Vladimir Golykhovsky described nicely how it was developed [1]. The consequences were relevant in paediatric orthopaedics, primary and secondary trauma care, and limb deformation from other disorders.

In paediatric orthopaedics the main applications were congenital, neurological [2] and post-infectious deformities. Primary trauma care now had a very versatile instrument for reconstruction of large bone and soft tissue loss [3]. But in secondary trauma care, the Ilizarov method has its major application. The combination of infection with open fractures, tissue loss, and subsequently compromised healing showed to be one of the most appealing applications. Post-traumatic deformity has always been a very difficult and challenging medical problem. When a primary treatment has an inadvertent outcome, the next step for an improvement of the situation usually is dealing with tissue loss and compromised healing of bone and soft tissues. The possibility of combining the resection of devitalised tissue, providing stability with the circular frame, and gradual tissue (bone and soft tissues) distraction is a real step forward. This treatment has provoked the claim that infection more or less "melts away", even without antibiotics, and this has acquired substantial support by angiogenesis studies [4, 5].

Other applications of callus distraction were further developed. New applications were found in bone diseases [6] as osteogenesis imperfecta [6-8], hypophosphatemic rickets [9] and skeletal dysplasia [10], in tumor resections [11-15] or treatment of tumorous conditions like Ollier's disease [6, 16, 17], congenital tibia pseudarthrosis [18-20], post-infectious joints destruction [21-25], chronic osteomyelitis [26], joint contractures [27-30], joint distraction for osteoarthritis [31-35], residual clubfoot treatment [36-42], short stature [43-50], even cosmetic limb lengthening [51]. Even soft tissues could be distracted, so soft tissue defects could be closed [52, 53]. One must bear in mind that all these have been explored by Ilizarov in earlier days [54-56], although this, at the time, hardly reached the broader orthopaedic community [57].

Advantages of bone regeneration by callus distraction for limb lengthening

The concept of callus distraction was not new. In 1905, Codivilla was the first to describe a limb lengthening procedure [58], Abbott, Anderson, Judet and Wagner

were later pioneers in this field [59-63]. These treatment attempts were initially fraught with complications, due to a lack of understanding of factors influencing the biological process of bone formation in the distraction hiatus and the soft tissues reactions to distraction. Since the introduction of the Ilizarov technique, it stopped to be a somewhat heroic enterprise and became a much more controllable and predictable treatment option for the severest of limb deformities [64-66]. It become clear that certain limitations from the past could be overcome and new horizons came in sight. This is best illustrated with the overwhelming number of papers that have been published since the introduction of the Ilizarov method in the western countries, not to mention the abundance of literature that has been published in the Soviet Union since the nineteen sixties, that was only discovered after the popularization of the Ilizarov method in the West.
The success of this new treatment appeared to be based on the following principles [52, 65, 67], as there are:

- Stability of the external fixator [68, 69],
- Axial motion of the bone thanks to the tensioned trans-osseous wires [70-72],
- Physiologic use of the lengthened limb [73, 74],
- Gradual lengthening after an interval of about a week after the osteotomy, the so-called 'latency period' [47, 75-77],
- A period of waiting for bony union, the 'consolidation period', without additional treatment like bone grafting [63],
- Special care to the osteotomy - 'corticotomy' [78-81],
- Compression on the bone ends [82],
- Versatility of the instrument; the circular external fixator, also named 'the frame'.

With fairly simple tools it became possible to correct multiplanar deformities with distraction, rotation, angulation, translation, sequentially or even at the same time [83, 84]. Nowadays, multiplanar and multidirectional correction is even simpler with the introduction of the Taylor spatial frame [85].

Disadvantages of callus distraction by the Ilizarov method
Despite its great success and the revolutionary treatment concept, there are disadvantages of the Ilizarov method as well.
One of the main problems is the bulkiness of the external fixator. Apart from all practical problems in wearing of clothes as well as moving around, patients as well as professionals have difficulties getting used to the sight of the limb, with pins sticking out or stabbing into it from all sides.
Another problem is caused by way the bone is fixed to the frame. Long, thin transfixation wires and Steinmann pins/half pins are used. Placement of the pins through the soft tissues is a difficult task, because transfixation means that one has

to consider the entry as well as the exit point of the wires. Improper placement of the pins and wires, mostly near the joints, leads to fixation of muscles and tendons, as well as kinking of the soft tissues over pins and wires during movement of the joints which in its turn causes considerable irritation of the tissues with discharge and infection as a resultant: 'unhappy pins'. Irritation and infection cause considerable pain, furthermore the patient tends to stop exercising the limb, which in its turn leads to joint contractures [86]. Neurovascular structures, muscles and tendons need to be avoided [87]. When correction starts, the transfixation wires are dragged through the soft tissues. Distraction can thus frequently be painful, because tissues are tensioned. In order to prevent contractures, the patient has to do exercises, which is painful again [88, 89].
The distraction of muscles and nerves causes biological changes that impair recovery after the lengthening procedure, diminish muscle strength [90-93] and neuropathy [94-99].
The duration of the treatment and considerable discomfort necessitate intensive aftercare for the patient. It is understandable that patients have coping problems with the situation [100]. A big effort is needed from the patient's environment too. Depression and other psychological problems occur during the treatment, but were shown to disappear quickly after the treatment [101].
The limbs that are going to be treated are usually not in a good shape. Atrophic and fibrotic muscles frequently accompany congenital deformations. A post-traumatic deformed leg has scarring from the trauma, the multiple operations afterwards and tissue loss causes dysfunction anyway.
Joints are frequently affected in congenital deformities [102-104]; instability due to congenital deformations such as congenital aplasia of cruciate ligaments [105-107] and hypoplasia of the lateral femoral condyle in the knee [108], dysplasia of the hip [109-111] and ball and socket joint in the ankle [112], or they may be contracted as well. The knee and ankle may be contracted in neurological and post-traumatic conditions. In all these situations (sub)luxation and (further) contracture are imminent when the bone is lengthened [111].

Another important factor to mention is that it is hard to predict the strength of bone. Much research has been done to estimate the strength of regenerated bone in the distraction callus, because a bone is susceptible to fracture or plastic deformation after removal of the frame [113-115]. Using mechanical analysis of the forces exerted on the circular external fixator during weight bearing, in vivo load sharing ratios could be calculated [116, 117]. Non invasive imaging techniques were tested for estimated strength of the distraction callus, some are easy to perform in outpatient clinic, for example standard radiographs [118], and ultrasound [119-123]; others are more demanding, for example bone densitometry [124] or CT scanning [125]. The result of these investigations is that patients with short stature are at higher risk for plastic deformation or fracture of the distraction callus. It seems to be possible making an estimation of the bone regenerate strength, but in general practice the external fixator is gradually made less rigid (dynamisation), and removed after 6-8 weeks. After removal the bone is temporarily protected with an orthosis or with a cast.

Delayed union and nonunion are greatly reduced with the Ilizarov techniques of compression and distraction, but it still can happen. Great effort is undertaken to get insight in the possible mechanisms of compromised union. Additional protocols have been tried to improve bone healing such as ultrasound [126], and bone grafts [63].
The complications are numerous in variety and severity; the complication rate is high [127, 128]. Meanwhile the learning curve is extremely long, and has been estimated to be up to 30 procedures [129]!

Aim of this thesis
Why are doctors undertaking these 'terrible' treatments? The answer is the outcome. The results of this treatment option in the *severest* of limb deformities are much better and more predictable than ever before. Usually, the starting point is a leg, not normally usable, with otherwise the forecast of an orthosis for the rest of life, orthopaedic shoes with high elevations, sometimes amputation [130], disturbed gait, limited ADL status.
So, the big issue is, what can be achieved [131-133], and at what cost [134-136]? What are the side effects, for example unexpected biological reactions to the inevitable trauma of treatment? When a bone is pierced, cut, and distracted, biological reactions are induced. A well known effect of femoral fracture is stimulated growth for a two year period [137-139]. This causes limb length discrepancy up to 2 centimetres. Do we provoke this reaction with a corticotomy also?
To answer these questions, the evaluation of the results of treatment leads to new understanding of possibilities and limitations. This is also the starting point for new goals.

Limb deformity correction has a long tradition in the University Medical Centre Utrecht. In the past reports of the results of limb reconstruction have been published [30, 32, 34, 35, 93, 101, 140-142]. Since the introduction of the Ilizarov method in 1990 in Utrecht, the application of the Ilizarov technique has been undertaken for several clinical problems; most notably ankle and knee joint distraction for post-traumatic osteoarthritis, the psychological impact of limb reconstruction with the Ilizarov method, severe joint contracture, paediatric limb reconstruction, post-traumatic limb reconstruction, failed knee arthrodesis after infected knee arthroplasty. The last three indications have not been evaluated so far; these are the basis of this thesis.

The following questions were formulated from the aforementioned considerations and are the basis for the aim of this thesis.

I. What are the results and complications of limb lengthening and reconstruction in growing individuals?

II. What is the effect of limb lengthening on the remaining spontaneous growth of the limb, and is any factor recognizable that might influence the growth rate during and after limb lengthening in growing individuals?

III. Can growth stimulation be exerted by application of a fixator to the femur with or without joint distraction during tibial lengthening.

IV. Can growth plate technetium scintigraphy be used as a predictor for the future growth rate.

V. Which are the results of limb lengthening and reconstruction in adult post-traumatic deformities?

VI. Is knee arthrodesis with the Ilizarov method a good option for the salvage of failed knee arthrodesis after infected knee arthroplasty?

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Chapter 2

Paediatric lower limb deformity correction using the Ilizarov technique: a statistical analysis of factors affecting the complication rate

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Abstract

Limb length discrepancy (LLD) and other patient factors are thought to influence the complication rate in paediatric) limb deformity correction. In the literature, information is conflicting. This study was performed to identify clinical factors that affect the complication rate in paediatric lower-limb lengthening. A consecutive group of 37 children was analysed. The median proportionate LLD was 15 (4–42)%. An analysis was carried out on several patient factors that may complicate the treatment or end result using logistic regression in a polytomous logistic regression model. The factors analysed were proportionate LLD, cause of deformity, location of corrected bone, and the classification of the deformity according to an overall classification that includes the LLD and all concomitant deformity factors. The median age at the start of the treatment was 11 (6–17) years. The median lengthening index was 1.5 (0.8–3.8) months per centimetre lengthening. The obstacle and complication rate was 69% per lengthened bone. Proportionate LLD was the only statistically significant predictor for the occurrence of complications. Concomitant deformities did not influence the complication rate. From these data we constructed a simple graph that shows the relationship between proportionate LLD and risk for complications. This study shows that only relative LLD is a predictor of the risk for complications. The additional value of this analysis is the production of a simple graph. Construction of this graph using data of a patient group (for example, your own) may allow a more realistic comparison with results in the literature than has been possible before.

Introduction

The Ilizarov leg lengthening procedure is a well-established treatment for limb length discrepancy (LLD) and complex limb deformities in children. Nevertheless, reported complication rates are high, suggesting that this type of treatment is

demanding on patients and medical staff [1–6].
It is well understood that the complexity of the deformity is related to the risk for complications, but how these relate numerically is not fully understood [1,7]. As the complication rate is an important outcome measure, limb reconstruction centres will always be interested in a comparison with other centres as a quality control. By analysing our paediatric patient group we wanted to identify the numerical relationship between LLD, concomitant deformity factors and the complication rate. In this process we aimed to create a graph that allows a visual representation of these relationships, which makes it a tool to clarify how a reconstruction unit performs.

Patients and methods

Patients

A retrospective study on 37 patients (20 girls) with LLD and/or concomitant deformities such as misalignment was performed. The aetiology of the LLD was congenital in 22 patients and acquired after trauma or infection in 15 patients. Of the patients, 33 had one or more concomitant deformity: 14 patients underwent 28 operations on the involved limb before the Ilizarov treatment. Absolute LLD was progressive with time in all patients.
An overview of the patient characteristics and the details of their deformities are given in Table 1.
In these 37 patients, 39 bone segments, 17 femoral and 22 tibial, needed to be corrected. The median age at the commencement of the treatment was 11 (6–17) years. The median preoperative LLD was 5.1 (1.7–17.9) cm, and the median proportionate LLD was 15 (4–42)%. Patients with lesser LLD had concomitant deformities that needed simultaneous correction.

Methods

Deformities were classified according to method adopted by Dahl et al. [1] When complete correction was not envisaged, a calculated residual deformity was accepted. In these patients, the residual deformity was not calculated as a complication. Ten patients had deformities that the procedure could not entirely correct: including problems mostly due to joint contractures and excessive LLD. Patient 9, having polyostotic fibrous dysplasia, a femoral fracture through the diseased bone, and a rotational deformity of the tibia, was considered to have undergone satisfactory treatment if consolidation of the femoral fracture and tibial axial correction with any amount of elongation could be achieved. Further, in patient 11 we anticipated an LLD of 1.5 cm, because the patient had a neurological drop foot. Large LLD – that is, more than 25% of the healthy bone – causes a higher risk for complications. Some authors, such as us, choose to lengthen in two steps in these patients. Therefore inequalization would not be considered as a

complication in patients 1, 4, 6, 9, 11, 19, 20, 27, 28 and 33.
In all procedures, axial correction and lengthening was performed by callus distraction using a classic Ilizarov circular fixator. After corticotomy, distraction was delayed for 5–7 days. The distraction rate was 0.25mm three to four times a day. After obtaining radiological evidence for the consolidation of the distracted callus, the frame was removed. Cast immobilization followed for 2–4 weeks. Finally, a brace was applied for 6–8 weeks. Weight bearing was encouraged during the treatment period, and physiotherapy was provided to prevent and/or treat joint contracture.
Complications of surgical correction were classified according to method used by Paley [3].
Relative LLD, bone lengthening, cause of deformity and the Dahl classification were included in the model for analysis of the influence on the complication rate, as these factors are frequently identified as causes of possible complications in the treatment [1,3,6,8,9].

Data analysis
Major determinants of the deformities such as large relative bone loss of the affected bone, site of the deformation, and cause of the deformity (either congenital or acquired) are suspected to affect treatment outcome negatively. Other coexisting deformities could influence the outcome as well and may be grouped in a classification as described by Dahl et al. [1]. To assess the relationship between these factors and the complication rate, a polytomous logistic regression approach was used. Instead of modelling the probability of 'complication' as a dichotomy, this approach models the probability of more than two ordered outcome categories simultaneously. The independent variables were all added to the model and then, in a backwards stepwise manner, the multivariately insignificant predictors were removed (relative LLD, bone lengthening, cause of deformity and severity of deformity according to the Dahl classification) [1].
The outcome variable was the count of the number of complications, and the model estimated the probability of observing zero, one or two complications as a function of the independent predictors.

Results
The median lengthening was 5 (1–8) cm, and the median percentage lengthening was found to be 14 (3–28)%. The median lengthening index was 1.5 (0.8–3.8) months per centimetre lengthening.
In 36 out of 37 patients the desired bone lengthening was achieved. In 10 patients, 14 additional surgical interventions were necessary to overcome obstacles and complications. All results are given in Table 2.

Problems
Bone lengthening was accompanied by 38 'problems'. Twenty-seven pin tract infections were successfully treated with oral antibiotics. In six cases, the duration of external fixation was prolonged because of delayed union. Four peroneal nerve dysfunctions, causing hypaesthesia in the foot, healed fully without further intervention. One joint contracture was effectively treated with physiotherapy.

Obstacles and complications
There were six obstacles and 21 complications in 37 lengthening procedures of 39 bone segments (69%). See Table 2.
In patient 22, lengthening was stopped 3 days after initiation because of a deep peroneal nerve palsy. After corticotomy, the tibia was acutely internally rotated by 30°. Despite cessation of lengthening, peroneal nerve function only partially recovered at final follow-up.
In three patients (7, 24 and 31) a fixation pin had to be removed because of persistent infection.
A fracture occurred in six patients (4, 9, 14, 15, 19 and 36) while the frame was on the leg or shortly after frame removal.
In two patients (6, 8) the femorotibial joint subluxated during femoral lengthening, and this was treated successfully by bridging the knee and by physiotherapy, respectively. Premature consolidation of the distraction zone required a recorticotomy in one patient (6).
Four patients (5, 6, 8 and 31) had persistent restriction of knee motion after the lengthening procedure. In these patients, peripatellar soft tissue release and surgical lengthening of the quadriceps tendon, followed by intensive physiotherapy, treated knee stiffness. At follow-up, the range of motion of the knee joint remained decreased by 20–25° in all four patients. Full extension, however, was possible in two patients and improved by 10° in the remaining two. In one patient (29), a nonunion in the tibia resulted from two bone grafting procedures.
The median number of operations was 2.4 (range 2–5) per patient, including the two operations to apply and remove the frame. The median residual LLD was 2.3 (minus 0.7–14) cm. The negative value indicated that the treated leg in one patient became 0.7 cm longer than the healthy leg. The median residual percentage LLD was 6 (minus 1–37)%.

Statistical analysis
The extent of the deformity influences the outcome, as indicated by Dahl et al. [1]. To assess the relationship between the deformity and the complication rate, an analysis was carried out by logistic regression in a polytomous ordinal regression model. This model is graphically represented with the relative risk for complications on the vertical axis and the proportion or percentage LLD at the

start of the treatment on the horizontal axis (Figure 1). The lines separate the risks for none, one, and two obstacles and/or complications, respectively. With this model, we try to clarify and visualize the relationship between the severity of the deformity and the proportionate risk for complications.
For example, from this graph one reads that the risk for one obstacle or complication is 50% when an LLD of 10% exists preoperatively.

Discussion
The outcome of lengthening procedures is determined from the occurrence of complications, whereas the incidence of complications is determined from the severity of the deformity. How these relate in numbers is not well known. In only one study, the occurrence of separate types of complications in relation to the lengthening percentage was calculated [8]. In our study, we tried to visualize the overall risk for complications in relation to the deformity with two purposes. First, we wanted to show the patient and the parents how many complications had to be anticipated before the treatment. Second, we wanted to generate an overall view for comparison between studies.
In our study, the complication rate was 69% for the obstacles and real complications, in accordance with that in the study by Paley [3]. Other studies reported complication rates of 46–130% when using the Ilizarov method [3,10–14]. Fractures occurred in six patients (16%) in our study, and this compares with 8–50% reported in the literature [9,15]. Joint problems such as contractures and (sub)luxation were seen in six patients (16%), 10–85% of which have been reported previously [10–14,16–20]. Bridging an unstable or contracted knee and/or ankle joint using the ring fixator may be helpful in preventing such complications [21]. Occurrence of other complications in our study such as premature consolidation (14%), delayed union (3%), angulation (13%), severe pin-site infection (8%) and nerve injury (3%) corresponds equally to that reported previously [9–14,16–20].

However, comparison is difficult because no uniform complication classification exists [16] and frequently only fragmentary information is available. Dahl et al. [1] suggested the use of percentage LLD to gain more insight into the severity of the deformity. When using this method, lengthening by more than 25% of the initial length proved to increase the risk for complications greatly, and it may even cause further growth inhibition as compared with preoperative growth retardation [11,12,17,21–27].
The overall complications rate in the present study seems to be at the same level as the results reported in the literature for limb reconstruction after paediatric lengthening [6,12]; however, we do not know whether our results are really comparable with the results from other limb deformity centres. The severity of the deformity is related to the complication rate [28,29], but only once quantified for

separate complications [8]. We hypothesized that a numerical relationship between the preoperative LLD data and the related complication rate could be shown combining both parameters in a PLUM ordinal regression model using logistic regression. From the acquired data, we constructed a simple graph to express the proportionate relationship between the rates of complications, as related to the percentage LLD (Figure 1). The graph shows weak relationship between proportionate LLD and complication rate in children, resulting in a shallow slope of the curves. In a previous study on post-traumatic limb reconstruction in adults, a stronger relationship was shown, with a steeper slope of the curves [30]. The difference between the present study and the aforementioned study [30] was not analysed, and may be a subject for further study, because it needs a different statistical approach. It may be speculated that the difference between children and adults is that a growing individual is biologically better equipped for soft tissue distraction than a fully grown person, simply because of the fact that the body of a growing individual is growing.

Conclusion

In this study, the complication rate of below 25% paediatric limb lengthening is not influenced by any investigated deformity factor. Complication rates in paediatric limb lengthening can be compared one on one between reconstruction units without a conversion factor for deformity factors. We hope that other authors are able to construct a similar graph to understand and make interpretations of their own results in relation to other studies.

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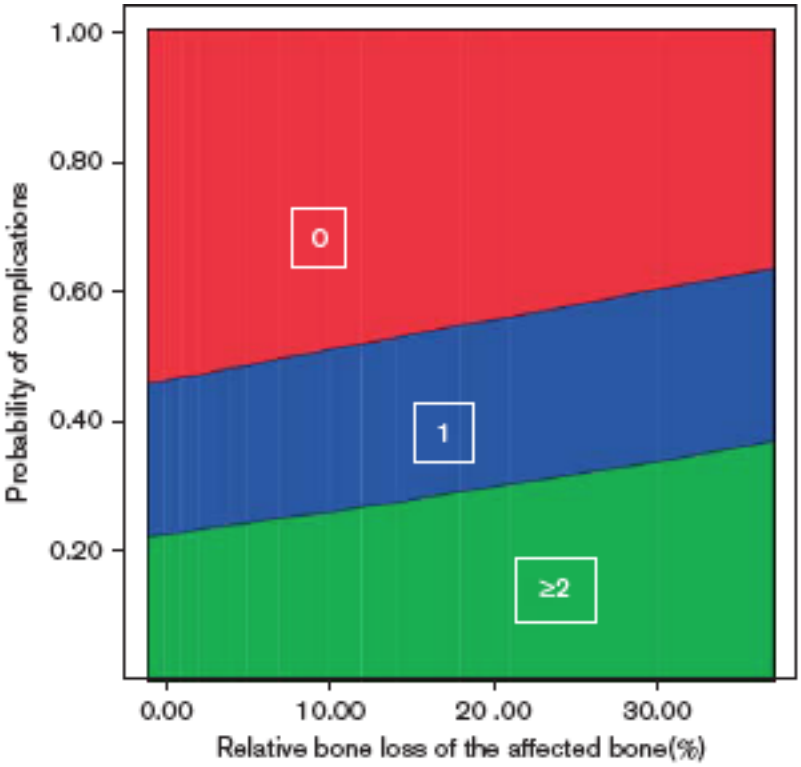

Figure. The risk for complications depends on percentage LLD in a logistic regression model. The y-axis represents the estimated probabilities of zero, one, two or more complications at a certain proportionate shortening of the affected bone (%), as represented on the x-axis. For example, the risk of encountering one or more complications is 50% for a bone loss of 10% in the affected bone. LLD, limb length discrepancy.

Patient	Gender	Age (years)	Location	Diagnosis	Concomitant deformities and factors (legend)	LLD (cm)	rLLD (%)	Angulation and rotation (degrees)	Dahl type
1	F	9	tibia	growth arrest after osteomyelitis proximal tibia	3,5,11,19,23	7	20	30 varus	4
2	F	17	femur	growth arrest after arthritis of the hip	19,23	4.1	9	40 varus	3
3	M	12	tibia	congenital short tibia	3,9,26,26	5.6	16		4
4	F	9	tibia	Femur-Fibula-Ulna syndrome	2,3,7,16,17,19	7.5	26	54 varus	5
5	M	16	femur	growth arrest after fracture distal femur		4.1	9		1
6	F	6	tibia	Femur-Fibula-Ulna syndrome	2,3,7,8,16,17,19,20,23	8.9	20	35 valgus, 45 int.rotation	5
7	F	9	tibia	congenital short tibia	6,8	6.1	23		3
8	F	9	femur	congenital short femur	16	5.1	16		2
9	M	14	femur + tibia	poly-ostotic fibrous dysplasia	2, 3, 14,20, 23,24,24, 28, 28	17.9	20	45 int. rotation tibia	5
10	F	9	femur	growth arrest after arthritis of the hip	1,3	4.3	13		2
11	F	11	tibia	child abuse ischiac nerve lesion	12	4.5	20		2
12	M	16	femur	congenital short femur		3.9	9		1
13	M	14	tibia	congenital short tibia	3,7,8,9,17	4.9	15		3
14	F	13	femur	congenital short femur	21	5.7	13		1
15	M	8	femur +tibia	congenital short femur + tibia	16	7.3	12		3
16	M	15	femur	congenital short femur	19	4.5	9	20 valgus	1
17	F	13	femur	growth arrest after fracture distal femur	2,4,11,19,20,23,23	4.4	11	10 valgus, 15 int. rotation	5
18	M	11	femur	growth arrest after arthritis of the hip	1,2,19,23,23,24	4.2	11	20 procurvatum	4
19	F	7	tibia	congenital short tibia	5,7,8,17,24,25,26	7.8	26		5
20	M	6	tibia	congenital short tibia	2,5,7,8,16,17,24,25	8.4	36		5
21	M	14	femur	congenital short femur	19,21,23	2.2	4	27 valgus	2
22	M	11	tibia	Ollier's disease	2,19,20	4.6	16	35 ext. rotation, 18 recurvatum	4
23	M	8	femur	congenital short femur	21,24,27	5.4	18		3
24	F	9	femur	growth arrest after arthritis of the hip	19	2.9	8	20 valgus	2
25	F	10	tibia	congenital short tibia	3,19	5.4	18	14 valgus	3
26	M	14	tibia	growth arrest after arthritis of the knee	19	3.9	7	20 valgus	2
27	M	7	tibia	congenital short tibia	3,7,16	8.9	33		4
28	F	6	tibia	congenital short tibia	3,7,8,16,19	10.2	42	25 procurvatum	5
29	F	16	tibia	growth arrest after fracture proximal tibia	13,19,20	2	6	24 valgus, 15 ext. rotation	3
30	F	8	tibia	congenital short tibia	7,15,18,19,23,23,24,26	1.7	6	30 procurvatum	4
31	M	11	femur + tibia	congenital short femur +tibia	16	7.7	10		3
32	F	14	femur	growth arrest after fracture distal femur		6	15		1
33	F	11	femur	growth arrest after arthritis of the hip	2,3,16,22	14.8	38		5
34	M	7	tibia	Femur-Fibula-Ulna syndrome	2,3,7,8,16,17,24,25	6.2	29		5
35	F	10	tibia	Ollier's disease	3,7,17,19,23	2.6	9	35 valgus	2
36	F	13	tibia	congenital short tibia		3.4	8		1
37	M	9	femur	congenital short femur	7,17,19	1.9	7	30 valgus	2

Table 1. Patient characteristics

Legend of concomitant deformities and factors according to Dahl et al. (1994): 1 contracture hip, 2 contracture knee, 3 equinus, 4 ankylosis knee, 5 ankylosis ankle, 6 tarsal coalition, 7 fibular hypo-/aplasia, 8 absence of footrays, 9 clubfoot, 10 rigid antepes adductus, 11 dislocated patella, 12 ischiac nerve lesion, 13 peroneal nerve lesion, 14 femoral pseudarthrosis, 15 tibial pseudarthrosis, 16 ACL aplasia, 17 ball and socket ankle, 18 active infection, 19 angulation deformity, 20rotational deformity, 21 dysplastic hip, 22 dysplastic lateral femoral condyle, 23 previous lengthening procedure, 24 previous correction osteotomy, 25 previous resection fibular fibrous band, 26 previous correction equinus deformity, 27 other previous soft tissue corrections, 28 simultaneous correction in two bone segments

LLD (cm)	leg length discrepancy (LLD) in centimetre
rLLD (%)	relative leg length discrepancy, see text for the definition
Dahl (type)	see text for the definition of the Dahl types of severity of deformity

Pat	Frame	Where OT	Consol (weeks)	Paley problem	complications obstacle	real	Gain (cm)	LI (mo/cm)	LLD (cm)	rLLD (%)	F-U (mo)
1	3	2	42	8			6	1.7	13	37	73
2	1	1	34	4,8			5	1.6	0	0	15
3	2	2	30	4,8			6	0.8	0.6	2	60
4	3	2	38	8	2	3,9,9	6,5	1.4	4.6	18	40
5	1	1	26			10	4	1.5	0	0	18
6	3	3	22	8	1,6		5	1.0	7.8	30	103
7	2	2	23		8		6	0.8	0	0	97
8	1	1	26	1,8		10	5,5	1.0	1.7	4	45
9	3	2	19	4,8,8		9	6	1.1	14	15	41
10	1	1	28	7,8		3	5	1.2	0.7	2	77
11	2	2	26	8			4	1.5	1.7	5	47
12	1	1	36	7,8			4,5	1.8	0	0	26
13	2	2	28	4			5,5	1.2	3.8	9	33
14	1	1	36			9	6	1.9	0	0	21
15	3	3	31		9	9	8	0.9	-0.7	-1	109
16	1	1	23	8			4	1.3	0.5	1	28
17	3	1	32	7,8			4	1.9	1	2	24
18	3	1	27	8			5,5	1.1	0.5	1	72
19	2	2	29	8		6,9	4,5	1.6	4.7	14	83
20	3	2	25	8			6	1.0	2.5	10	32
21	1	1	33	7,8		6	2	3.8	2.5	5	15
22	2	2	8	7,8		3,4,6	1	2.0	4.4	15	64
23	1	1	21	8			5	1.0	-05	-1	99
24	1	1	22	7	8	3	2	2.0	2	5	60
25	2	2	32	8			5	1.5	0.5	2	55
26	2	2	20	8		6	2	2.5	2.7	7	24
27	3	2	27	8			6	1.0	4	14	63
28	3	2	25				6	1.0	4.2	12	96
29	2	2	27	8		1,7	2	3.0	0	0	6
30	3	3	11	8			1	2.5	0.9	3	65
31	3	3	30	8	8	10	8	1.0	0	0	66
32	1	1	35				6	1.5	0	0	43
33	3	1	30	8			6	1.1	8.4	21	48
34	3	2	36	8			6	1.0	0	0	62
35	2	2	31			3,6	2	3.0	0	0	102
36	2	2	33			9	3	2.6	1	2	49
37	1	1	28				2	3.3	0	0	28

Table 2. Results of limb deformity correction in 37 patients.

Legend

Frame	configuration of Ilizarov frame: 1 femur, 2 tibia, 3 femur and tibia
Where OT	osteotomy site: 1 femur, 2 tibia, 3 femur and tibia
Consol	consolidation time in weeks, duration of correction and consolidation, total period in frame.
Paley complications	problems (difficulties resolve without operation), obstacles (difficulties resolve with operative intervention), minor and major complications (all intra-operative injuries; difficulties not resolved before the end of the treatment, minor complication if resolved with non operative treatment, major complication if operative treatment is required): 1 muscle contracture, 2 joint luxation, 3 axial deviation (minor <5°, major >5°), 4 neurologic injury (peroneal nerve), 5 vascular injury (compartment syndrome-fasciectomy), 6 premature consolidation, 7 delayed consolidation, 8 pin-site problems, infections, 9 refracture, 10 joint stiffness
LI	lengthening index; period in frame (months) divided by length (cm) gained
LLD (cm)	residual leg length discrepancy in centimetre
rLLD (%)	residual relative leg length discrepancy, see text for the definition of relative LLD
F-U	follow up in months after initiation of treatment

Chapter 3

Growth rate after limb deformity correction by the Ilizarov method with or without knee joint distraction
Lengthening in 30 children followed for at least 2 years

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Abstract

Background and purpose Growth inhibition and stimulation have both been reported after juvenile limb lengthening. Distraction of a joint usually suspends and unloads the growth plate and may stimulate growth. We investigated the influence of knee joint distraction on the growth speed after limb lengthening.

Methods In a retrospective study, growth patterns were analyzed in 30 children mean 61 (24-109) months after limb lengthening with the Ilizarov method, each child having more than 2 years of remaining growth. In 14 patients with knee joint instability, the knee was bridged over during lengthening for joint stabilization. Whether or not joint bridging and distraction would affect growth of the lengthened limb by unloading the growth plate was evaluated with a repeated measurements analysis of variance.

Results After lengthening procedures, the proportionate leg length discrepancy was found to decrease in 16 patients, suggesting an increased growth rate in the lengthened limbs. A statistically significant faster growth rate was seen in 8 of 14 patients with knee distraction as compared to patients with single bone frame configurations.

Interpretation Further research is required to investigate whether growth stimulation is due to the surgical technique and whether joint distraction should be recommended during limb lengthening in growing children.

Introduction

The Ilizarov leg lengthening procedure is a well-established option in the treatment of limb-length discrepancy. Soft tissue tension resulting from the resistance of muscles developed during distraction may cause (sub) luxation and/or contracture in abnormal joints [1-3]. Moreover, due to this soft tissue tension, pressure forces on the adjacent physeal and articular cartilage may jeopardize the structure and function of these cartilaginous tissues, affecting growth and inducing degeneration of the joint cartilage [4-9]. To prevent such complications, a joint can be bridged and distracted during the lengthening procedure. Repeated joint distraction may prevent associated complications or even cause increased growth [10].

We evaluated the possible long-term effect of lengthening and joint distraction on the growth pattern of the lengthened limb, as this may influence further decisions about treatment.

Patients and methods

Patients

30 patients (16 girls) underwent lengthening procedures with the Ilizarov method (Table 1). 33 bone segments, 12 femoral and 21 tibial, were corrected. In 3 patients, the femur and tibia were corrected simultaneously (patients 4, 11 and 25). The mean age at the start of the treatment was 10 (6-15) years.

Deformity and classification

The mean preoperative Leg Length Discrepancy (LLD) was 6.3 (1.9-18) cm, and the mean percentage LLD was 18 (6-42)%.
The severity of the deformities was classified in five types according to Dahl et al. [11] Type 1 indicates less than 15% LLD; type 2: 16-25%; type 3: 26-35%; type 4: 36-50%; and type 5: more than 50% LLD. The type of severity increases one level when 2 greater risk factors (e.g. congenital origin of the deformity, previous lengthening, multisite correction) are present, and when 3 lesser risk factors (e.g. pre-existent joint contracture, neurologic deficit, location of the deformity in the femur or foot) are present. The deformity in our study population was classified as deformity type 1 in 2 children; type 2 in 7; type 3 in 6; type 4 in 6; and deformity type 5 in 9 children.

Methods

Preoperatively, the length discrepancy was calculated from a single length measurement, which is sufficient for an accurate prediction of the future leg length discrepancy [12]. The measurement was made on standing AP radiographs, which are reliable for length measurements [13].
In all procedures, bone lengthening was performed by callus distraction with an Ilizarov ring fixator after a corticotomy. At the end of the operation, to prevent (sub) luxation, contracture, or potentially harmful pressure on articular and physeal cartilage (due to high tensile forces found in the soft tissues following lengthening [9, 14], knee joints were bridged and the knees distracted in 14 patients for about 1-2 mm after application of the frame under direct fluoroscopic control. After corticotomy, distraction was delayed for 5-7 days. Distraction was 0.25 mm, 3-4 times a day.
In the outpatient clinic, the patients were seen at 2- to 3-weeks intervals during lengthening and every 4-6 weeks during the consolidation phase. Joint distension was controlled on the X-rays at every visit. If there was any reduced distension, the joint was distracted to such an extent that the primary radiological joint distension was regained. This procedure was repeated as required during the whole period of frame application. After

radiological evidence of consolidation of the distraction callus, the frame was removed. Cast immobilization was applied for 2-4 weeks and a brace was given for another 6 - 8 weeks. Weight bearing was encouraged during the treatment period and physiotherapy was given. If needed, psychological support was provided to patient and family [15].

Growth pattern

At least 2 orthoradiographs for leg length measurements were performed after removal of the Ilizarov frame to evaluate further growth in length in both lower limbs. These measurements were performed after mean 61 (24-109) months. All patients had more than 24 months of remaining growth after Ilizarov treatment. The decision to select this term was because bony interventions or fractures of the limb may lead to locally, although temporary (less than 2 years) increased growth [16-18] Since we wanted to know whether knee joint distraction had any additional effect to the growth pattern, we had to look beyond 2 years after the start of the treatment.
To calculate the growth of the treated limbs, gain in length from the distraction -calculated between osteotomy ends- was deducted from the leg-length measurements after the Ilizarov procedure. Accordingly, any change in the proportionate (%) limb length discrepancy would identify a change in the growth rate.

Data analysis

Aguilar et al. reported that growth patterns can be predicted very accurately with a single limb-length measurement by a multiplier method [12, 19, 20]. From these data, we interpreted that limb-length discrepancy expressed as the ratio of the length of the long (usually normal) limb and of the shortened limb is a constant measure. In a graph in which the x-axis represents the length of the long (normal) leg and the y-axis represents the length of the shortened leg, the constant ratio (proportionate LLD) is expressed by a straight line with a slope identical to the ratio. After intervention, the slope of this line may change in the sense that an increased growth of the lengthened leg results in a steeper line (negative intercept, of the line with the y-axis) and a decreased growth in a shallower line (positive intercept, of the line with the y-axis). (Figure).
Since we only have one measurement before the intervention, the slope of the line before the intervention is not known. However, due to the reasonable assumption that the growth ratio is constant, considering the very accurate multiplier findings of Paley et al. [20], this line should go through the origin. Hence, as a proxy to the test whether the slopes before and after intervention are different, we can simply test whether the

regression line after intervention has an intercept above or below the origin (corresponding to a reduced or increased growth speed, respectively).
Data were analyzed by a repeated measurements analysis of variance using a Mixed Model in SPSS version 12.0.1. Repeated measurements were obtained over the follow-up time. The subject is a random factor within which multiple observations (follow-up moments) are nested. The normal limb is entered as a covariate (the x-axis) and the other limb's length is used as outcome variable. Each child contributes a varying number of observations over follow-up time. All factors except the subject were taken as fixed effects. Thus, the estimated slope and intercept are calculated as a common, fixed effect. We do not assume any specific model for the outcome itself, but the correlation of repeated measurements is assumed to be of autoregressive type (order 1). A p-value of less than 0.05 was considered statistically significant. The primary parameter of interest is the estimated intercept itself and not the slope of the regression line (see Figure 1 and the explanation given above).
We analyzed different variables that may influence growth. Type of frame (mono-osteal: femur or tibia compared with poly-osteal with bridged and distracted knee), location of osteotomy (femoral, tibial, or both) and type of deformity (congenital, acquired). These variables were entered as categorical covariates. In case of 3 or more categories, an overall test was first performed; only if that effect was significant, multiple comparisons were performed to compare the various subgroups. All effects and the associated 95% confidence intervals were estimated from these models.

Results

The mean lengthening was 4.8 (1-8) cm, and the mean percentage lengthening was found to be 14 (3-28). The mean lengthening index was 1.5 (0.8-3.3) months per centimetre of lengthening (Table 2).

Growth patterns

In 16 patients, the proportionate shortening of the shortened leg decreased. Five patients had stabilized proportionate shortening and 9 patients had increased proportionate shortening. Frame configuration is the most important for growth rate. Frames with knee bridging were associated with an increased growth rate as compared to mono-osteal frames (Tables 3 and 4-A). Even so, not all patients with knee bridging experienced growth stimulation (only 8 from 14 patients), 1 patient had unchanged growth, and 5 of the 14 patients with knee distraction showed growth inhibition. Cause of LLD, site of osteotomy had no statistically significant association with growth patterns of the leg, except the tibial growth, which was significantly different after tibial osteotomy (Tables 3 and

4-B). All osteotomies caused growth inhibition, but tibial osteotomy caused almost none compared to femoral osteotomy or combined femoral and tibial osteotomy.

Discussion

The finding of increased growth after a limb lengthening procedure has been rarely reported. Increased growth has already been registered in 1 patient after a limb lengthening procedure [21] and for 2 other lengthened legs, the feet were reported to grow stronger after the lengthening procedure [22]. Growth stimulation has been reported in a limited number of studies after femoral lengthening in 2 studies [23, 24]. Group effects have not been reported [23-26]. It is known that after a femoral fracture, growth in the length of the traumatized leg may increase temporarily, but this effect always lasts for less than two years after the trauma [17, 18].

The definition of growth stimulation is important to explain our results. Usually, untreated shortened limbs show an increasing absolute shortening due to a general inhibition of the growth. At the same time, the proportionate (percentage) length discrepancy remains unchanged. Growth stimulation in the shortened leg is a change in the growth trend that results in a decreasing proportionate length discrepancy. When there is mild proportionate growth stimulation, the absolute shortening may increase during further growth simultaneously. Our finding of an increased growth rate for more than 2 years is not easy to explain. Our reason for unloading of the growth plate and joint cartilage was to protect these tissues against compressive forces by knee joint distraction during the lengthening procedure. This concept is supported by an experiment in rabbits with Achilles tenotomy to unload the tibial growth plates during lengthening [27]. Gradual distraction of the knee joint may act as a mild form of chondrodiastasis as suggested by De Bastiani [28]. Change in the growth program of the physis is inducedby an unknown mechanism.

We visually controlled distraction with fluoroscopy during the operation and later on with radiographs at intervals. We were unable to measure the compression or distraction forces acting upon the physes, so we could not verify whether the unloading of the physes was maintained continuously. One reason for not all children experiencing an enhanced growth rate may be that we were not able to control joint distraction on a continuous basis. Uncertainty remains as to whether growth patterns are predictable or variable, especially after lengthening or other interventions. Aguilar et al. showed that growth patterns could be calculated accurately and predicted with a single preoperative length measurement [12, 19]. Paley et al. also showed that growth patterns remain constant, and are independent from diagnosis, treatment, race, continent, historical period, chronological age and skeletal age [12, 19, 20, 29, 30]. These data were compared to the gold standard of the Anderson and Green data [31, 32], but also to many other databases of clinical and anthropological measurements. Consequently, it must be assumed that growth patterns remain predictable after lengthening, after epiphysiodesis, in congenital limb length discrepancy, and in skeletal dysplasia, because there is little variation in the outcome. As has been shown by several authors, this does not apply to growth patterns after fractures; in this situation, growth is only temporarily stimulated and becomes normal in less than 2 years [17, 18]

Unreliability of length measurements may influence the growth patterns seen. Even so, in centers with experienced personnel such as ours, the reliability of the measurements is usually within a few millimetres [13]. This corresponds to about 1% error in proportionate LLD, because it represents between 2 and 5 mm bone length (depending on the bone length: 20 centimetres for a very short tibia to 50 centimetres for normal femurs). So, the calculated average changes of 4% in our children means somewhere between 8 to 20 mm. If we take into account that lengthening in many cases causes further growth retardation [21, 24, 26, 33-35], we have observed a remarkable effect.

Further studies are required to confirm our findings of enhanced growth after the use of knee joint distraction during lengthening procedures, and to find out whether bridging and distracting the knee joint can be recommended in Ilizarov treatment to prevent complications and to stimulate physeal growth. Joint distraction as a single treatment in growing individuals may be considered in the future for the treatment of limb length discrepancy, and should be investigated. Continuous monitoring of the forces acting upon the physes may be an important parameter to investigate, because we found indirect evidence that unloading the physes causes stimulated growth. Decreasing proportionate length discrepancy as a biological phenomenon is very intriguing and difficult to explain.

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Patient	Gender	Age (years)	Location	Diagnosis	Concomitant deformities and factors (legend)	LLD (cm)	rLLD (%)	Angulation and rotation (degrees)	Dahl type
1	F	9	tibia	growth arrest, osteomyelitis proximal tibia	3,5,10,17,21	7	20	30 varus	4
2	M	12	tibia	congenital short tibia	3,9,24,24	5,6	16		4
3	F	9	tibia	Femur-Fibula-Ulna syndrome	2,3,7,14,15,17	7,5	26	54 varus	5
4	F	6	tibia	Femur-Fibula-Ulna syndrome	2,3,7,8,14,15,17,18,21	8,9	20	35 valgus, 45 int. rotation	5
5	F	9	tibia	congenital short tibia	6,8	6,1	23		3
6	F	9	femur	congenital short femur	14	5,1	16		2
7	M	14	femur+tibia	poly-ostotic fibrous dysplasia	2, 3, 12,18, 21,22,22, 26, 26	17,9	20	45 int. rotation tibia	5
8	F	9	femur	growth arrest after arthritis of the hip	1,3	4,3	13		2
9	F	11	tibia	child abuse ischiac nerve lesion	11	4,5	20		2
10	M	14	tibia	congenital short tibia	3,7,8,9,15	4,9	15		3
11	M	8	femur +tibia	congenital short femur + tibia	14	7,3	12		3
12	M	15	femur	congenital short femur	17	4,5	9	20 valgus	1
13	F	13	femur	growth arrest after fracture distal femur	2,4,10,17,18,21,21	4,4	11	10 valgus, 15 int. rotation	5
14	M	11	femur	growth arrest after arthritis of the hip	1,2,17,21,21,22	4,2	11	20 procurvatum	4
15	F	7	tibia	congenital short tibia	5,7,8,15,22,23,24	7,8	26		5
16	M	6	tibia	congenital short tibia	2,5,7,8,14,15,22,23	8,4	36		5
17	M	11	tibia	Ollier's disease	2,17,18	4,6	16	35 ext. rotation, 18 retrocurvatum	4
18	M	8	femur	congenital short femur	19,22,25	5,4	18		3
19	F	9	femur	growth arrest after arthritis of the hip	17	2,9	8	20 valgus	2
20	F	10	tibia	congenital short tibia	3,17	5,4	18	14 valgus	3
21	M	14	tibia	growth arrest after arthritis of the knee	17	3,9	7	20 valgus	2
22	M	7	tibia	congenital short tibia	3,7,14	8,9	33		4
23	F	6	tibia	congenital short tibia	3,7,8,14,17	10,2	42	25 procurvatum	5
24	F	8	tibia	congenital short tibia	7,13,16,17,21,21,22,24	1,7	6	30 procurvation	4
25	M	11	femur + tibia	congenital short femur +tibia	14	7,7	10		3
26	F	11	femur	growth arrest after arthritis of the hip	2,3,14,20	14,8	38		5
27	M	7	tibia	Femur-Fibula-Ulna syndrome	2,3,7,8,14,15,22,23	6,2	29		5
28	F	10	tibia	Ollier's disease	3,7,15,17,21	2,6	9	35 valgus	2
29	F	13	tibia	congenital short tibia		3,4	8		1
30	M	9	femur	congenital short femur	7,15,17	1,9	7	30 valgus	2

Table 1.

Legend:

concomitant deformities and factors according to Dahl et al. [11]:

1 contracture hip, 2 contracture knee, 3 equinus, 4 ankylosis knee, 5 ankylosis ankle, 6 tarsal coalition, 7 fibular hypo-/aplasia, 8 absence of foot rays, 9 clubfoot, 10 dislocated patella, 11 ischiatic nerve lesion, 12 femoral pseudarthrosis, 13 tibial pseudarthrosis, 14 ACL aplasia, 15 ball and socket ankle, 16 active infection, 17 angulation deformity, 18 torsion deformity, 19 hip dysplasia, 20 lateral femoral condyle dysplasia, 21 previous lengthening procedure, 22 previous correction osteotomy, 23 previous resection fibular fibrous band, 24 previous correction equinus deformity, 25 other previous soft tissue corrections, 26 simultaneous correction in two bone segments

LLD (cm)	leg length discrepancy (LLD) in centimetre
rLLD (%)	relative leg length discrepancy, see text for the definition
Dahl (type)	see text for the definition of the Dahl types of the severity of the deformity

Pat	Frame	OST	Consol	Paley	complications		Angulation	Gain	Gain	LI	LLD	rLLD	F-U	DLLD po	Growth
		site	(weeks)	problem	obstacle	real		(cm)	(%)	(mo/cm)	(cm)	(%)	(mo)	(cm)	rate
1	3	2	42	8				6	17	1.7	13	37	73	3	n
2	2	2	30	4,8				6	17	0.8	0.6	2	60	0.1	p
3	3	2	38	8	2	3,9,9	50° varus	6.5	23	1.4	4.6	18	40	4.5	n
4	3	3	22	8	1,6			5	11	1.0	7.8	30	103	0	p
5	2	2	23		8			6	23	0.8	0	0	97	2	p
6	1	1	26	1,8		10		5.5	17	1.0	1.7	4	45	3.3	n
7	3	2	19	4,8,8		9		6	7	1.1	14	15	41	6.4	n
8	1	1	28	7,8		3	14° valgus	5	15	1.2	0.7	2	77	-0.3	p
9	2	2	26	8				4	18	1.5	1.7	5	47	0.5	o
10	2	2	28	4				5.5	17	1.2	3.8	9	33	-0.7	p
11	3	3	31		9	9		8	13	0.9	-0.7	-1	109	0.6	p
12	1	1	23	8				4	8	1.3	0.5	1	28	0	p
13	3	1	32	7,8				4	10	1.9	1	2	24	0	p
14	3	1	27	8				5.5	14	1.1	0.5	1	72	1.5	n
15	2	2	29	8		6,9		4.5	15	1.6	4.7	14	83	-0.7	p
16	3	2	25	8				6	26	1.0	2.5	10	32	2.3	o
17	2	2	8	7,8		3,4,6	16° retrocurvatum	1	3	2.0	4.4	15	64	5.9	n
18	1	1	21	8				5	17	1.0	-0.5	-1	99	3.5	n
19	1	1	22	7	8	3	20° procurvatum	2	6	2.0	2	5	60	3.1	n
20	2	2	32	8				5	17	1.5	0.5	2	55	2	o
21	2	2	20	8		6		2	4	2.5	2.7	7	24	0.1	p
22	3	2	27	8				6	22	1.0	4	14	63	0.4	p
23	3	2	25					6	25	1.0	4.2	12	96	1.7	p
24	3	3	11	8				1	4	2.5	0.9	3	65	4.3	n
25	3	3	30	8	8	10		8	10	1.0	0	0	66	0.6	p
26	3	1	30	8				6	15	1.1	8.4	21	48	2.1	p
27	3	2	36	8				6	28	1.0	0	0	62	0.5	p
28	2	2	31			3,6	10°valgus	2	7	3.0	0	0	102	0	o
29	2	2	33			9		3	7	2.6	1	2	49	1	p
30	1	1	28					2	7	3.3	0	0	28	0	o

Table 2.

Legend:

Frame	configuration of Ilizarov frame: 1 femur, 2 tibia, 3 femur and tibia
OST site	osteotomy site: 1 femur, 2 tibia, 3 femur and tibia
Consol	consolidation time in weeks, duration of correction and consolidation, total period in frame.
Paley complications	problems (difficulties resolve without operation), obstacles (difficulties resolve with operative intervention), minor and major complications (all intra-operative injuries; difficulties not resolved before the end of the treatment, minor complication if resolved with non operative treatment, major complication if operative treatment is required): 1 muscle contracture, 2 joint luxation, 3 axial deviation (minor <5°, major >5°), 4 neurological injury (peroneal nerve), 6 premature consolidation, 7 delayed consolidation, 8 pin-site problems, infections, 9 re-fracture, 10 joint stiffness
LI	lengthening index; period in frame (months) divided by length (cm) gained
LLD (cm)	residual leg length discrepancy in centimetres
rLLD (%)	residual relative leg length discrepancy, see text for the definition of relative LLD
F-U	follow up in months after initiation of treatment
ΔLLD po	difference of LLD from first and last leg length measurement in cm
Growth rate	p stimulation, o neutral, n decreased growth rate

Table 3

Results from statistical testing by use of repeated measurements ANOVA mixed model. Significance of the possible treatment factors that may influence the growth pattern of the limb. The results of significant factors are elaborated in table 4.

Frame configuration on the whole leg	P = <0.01
Location of osteotomy on the whole leg	P = 0.97
Cause of deformity on the whole leg	P = 0.81

Location of osteotomy on the femur	P = 0.09
Location of osteotomy on the tibia	P = 0.04

Table 4-A

Results from statistical testing by use of a repeated measurements ANOVA mixed model. The frame configuration has a significant effect on growth pattern. The negative intercept of a knee bridging intercept indicates a decreasing proportionate leg length discrepancy, i.e. stimulated growth.

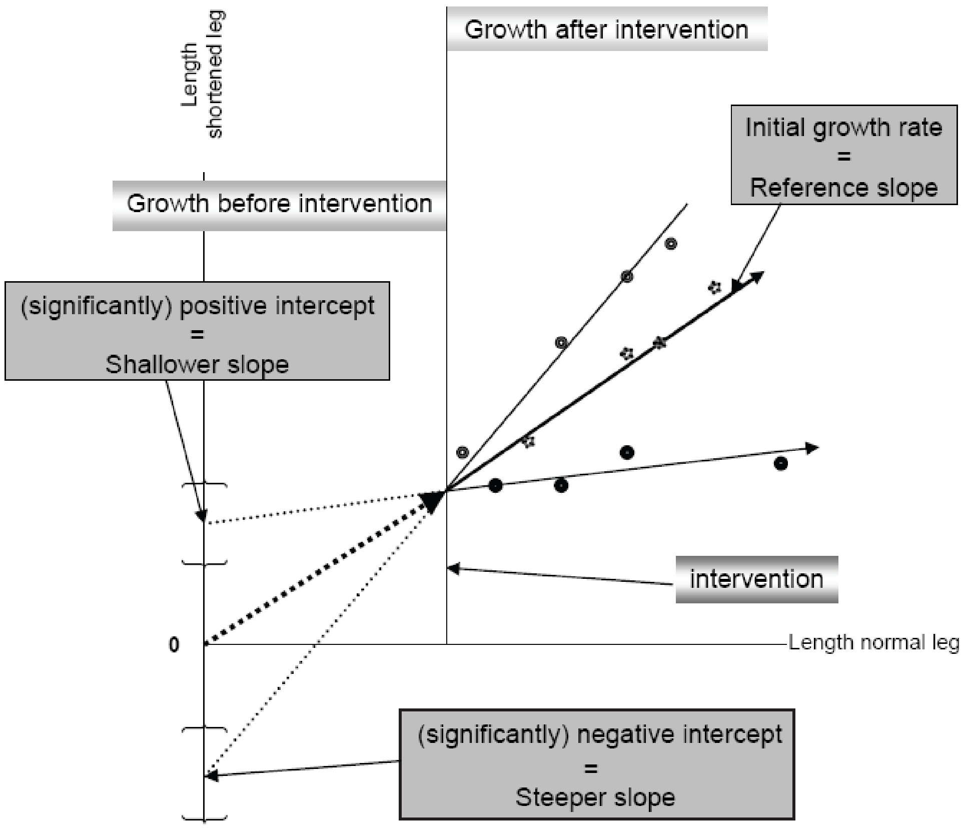
Frame configuration: $p < 0.01$			
Intercept femoral frame	+3.1	(-2.0 – +8.2)	95% CI
Intercept tibial frame	+3.3	(-1.5 – +8.1)	95% CI
Intercept knee bridging frame (#)	- 1.7	(-6.1 – +2.6)	95% CI

(#) category differs significantly from the other two categories

Table 4-B

Results from statistical testing by use of a repeated measurements ANOVA mixed model. The location of the osteotomy for the lengthening procedure has a significant effect on the growth pattern. The positive intercept indicates an increasing proportionate leg length discrepancy, i.e. inhibited growth in all osteotomy types. The tibial osteotomy has significant less inhibiting effect than other osteotomy types.

Location of osteotomy on the tibia: $p = 0.04$			
Intercept femoral osteotomy	+4.0	(+0.5 – +7.6)	95% CI
Intercept tibial osteotomy (#)	+0.7	(-9.9 – +11.0)	95% CI
Intercept osteotomy of femur and tibia	+3.6	(-2.6 – +4.1)	95% CI



(#) category differs significantly from the other two categories

Figure
Graphical representation of the statistical principle of a positive and negative intercept as the result of an intervention in a shortened leg compared with the normal leg.
The length of the normal leg is represented on the X-axis. The length of the shortened leg is represented on the Y-axis. The reference line represents the relation of length of the normal and shortened leg. The relation of the length of normal and shortened leg may change, for example by a surgical intervention. For better graphical representation, the gain in length from the lengthening procedure is deducted from the length of the shortened leg after the intervention.
When the line of proportionate growth shows a changed slope after the intervention as compared to the reference line, and when this new line has a <u>negative</u> intercept with the Y-axis, it represents increased growth of the shortened leg compared to the normal leg. When this new line has a <u>positive</u> intercept with the Y-axis, it represents decreased growth of the shortened leg compared to the normal leg.

Chapter 4

Can growth stimulation be exerted by application of a fixator to the femur with or without joint distraction during tibial lengthening?

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Submitted

Abstract

Purpose Data from our clinic showed that growth was regularly increased after application of a femur and tibia external fixator and knee joint distraction as a part of limb lengthening in children. Knee bridging by bi-osteal external fixation, and simultaneous distraction to protect the growth plate against damaging compression forces during lengthening, was performed to stabilize congenital instable joints. We wanted to check whether stimulated growth could be reproduced in a controlled experimental limb lengthening setting.

Methods A study with immature New Zealand white rabbits was designed to investigate the effects the tibial growth rate of tibial lengthening combined with knee joint arthrodiastasis by a femoral external fixator.

Results The results show that, on top of the pre-existent growth trend of the lengthened tibia, extra growth of the tibia was observed when a femoral external fixator was used, as compared to single tibial lengthening (p = 0,04). Whether the tibial external fixator was connected to the femoral fixator for joint distraction or disconnected, growth stimulation was observed in both study groups. A hint of further extra growth was seen in mild knee joint distraction, but this effect was statistically not significant.

Conclusions Since limited information exists about growth patterns of the paediatric limb after limb lengthening these findings are new. The preliminary conclusion is that the factors that are causing growth

stimulation are less likely non-mechanical, and more likely vascular and/or biochemical. Further investigations in this animal model may provide new information about the factors influencing bone growth stimulation.

Introduction

Callus distraction with the Ilizarov circular external fixator is an established limb lengthening method in children. Bridging of the knee joint during such procedures can prevent joint dislocations, contractures, and protect joint cartilage [1,2]. This technique may alter forces and the biological reaction to the trauma of the treatment in the lower limb and its growth plates, either by placement of pins in femur and tibia, or by the distracting forces to the growing bone.

We found additional growth in 8 out of 14 children with bridging of the knee in a group of 30 growing patients [3]. This additional growth persisted more than 2 years after a limb lengthening procedure.

We hypothesized that this additional growth is related to the application of femoral frames and/or knee arthrodiastasis with bridging the knee. Therefore, an animal study with tibial lengthening was designed to compare the effects of knee arthrodiastasis and placing bone pins in a sham operation.

Methods

Experimental design

The study contained three groups (Figure 1). Nineteen 8-week-old New Zealand white rabbits were operated. A circular tibial and a semi-circular femoral external fixator (EF) were developed for the experiment. Articulating distractors allowed 90° knee flexion (Figure 2).

Tibial lengthening started 3 days after the operation, which was done at the age of 8 weeks. The tibial EF was lengthened for 20 millimeter, which is about 25% of the tibial length, in daily increments of 1 millimeter. Further lengthening may cause growth inhibition [5]. Maintenance of the knee joint distraction was checked on radiographs. Distractions and lengthening could be performed without any need for sedation or pain relief.

Under sedation, 1 pre-operative and 15 follow up tibial length measurements were done by a calibrated plain anterior-posterior radiograph of both tibiae: weekly at age 9 – 18 weeks, biweekly at age 20 - 24 weeks, and every 4 weeks at age 28 and 32 weeks. See the timeframe of the study in figure 3. Tibial length was measured on postero-anterior radiographs for which the rabbit was positioned in a specially designed device with a radiopaque ruler. Length measurements of the femur were not included in the experiment, because the femora could not reliably be positioned in the measuring device in a test setting.
The radiographs were scanned, digitalized and read using the NIH Image 1.60 software package for Apple.
When the distraction zone consolidated, the external fixators were removed. Investigations were stopped when the rabbits were fully grown at the age of 32 weeks.
A pilot study in 1 rabbit was done to check whether the animals could undergo the experiment and to check whether arthrodiastasis could be created (Figure 4). Approval of the local institutional review board was acquired after the positive result of the pilot study.

Surgical procedures
All external fixators were placed on the left hind limb. The tibia was fixed to the frame on each ring with 2 crossed 1 mm Kirschner wires. The femur was fixed to the frame with 2 crossed 1 mm K-wires distally and 1 lateral 2 mm half pin proximally. The distracting knee articulator was placed just posterior to the anatomical flexion/extension axis of the knee, which resulted in further distraction when the rabbit flexes the knee. The tibia was subperiosteally osteotomized in the diaphysis. All steps of the operation were controlled with fluoroscopy.

Statistical methods
Means, standard deviations, frequency tables and cross tabulations whenever appropriate give the basic description of the data. For the purpose of comparing the three groups of animals, a linear mixed model was used (SPSS version 11.0). A regression model predicting the outcome in the left tibia length as a function of the group while adjusting for the right tibial length, time and time-squared was used.
For the analysis of relative length growth, the outcome variable was the length of the left tibia. Comparison of groups was restricted to time points above 11 weeks, after the lengthening procedure was stopped ("run-in" period). Continuous covariates were time (and time-squared to allow for proper modelling of the non-linear time effect) and the length

of the right tibia. As a fixed factor the grouping variable (3 levels) was used. Since the ordering of the three subgroups was made a priori according to the increase of the anticipated effect, a trend test was used to assess significance of the group effect. The predicted effect deduced from this mixed model was used to generate the appropriate graphics. The animal was introduced in the model as a random subject-effect (covariance matrix taken to be the identity in view of the low number of observations).

Results

5 animals in group 1, 4 in group 2, and 6 in group 3 completed the experiment. Fracture of the left femur shortly after surgery necessitated euthanasia in 3 rabbits. One animal failing to thrive was euthanized also. The external fixators were removed 3 months after surgery.

The resulting tibial length difference was calculated for each group as mean values as in figure 5A, and visualized in Figure 5B according to our statistical model. If the graph would be shown with representation of the standard deviations, it would make an unreadable graph.

In group 1, the lengthening of 20 mm in the distractor effectuated in about 17 mm mean tibial lengthening. The mean tibial length discrepancy after lengthening increased 2.3 mm and 2.8 mm in groups 2 and 3 respectively as compared to group 1, indicating extra growth as compared to single tibial lengthening.

The p-value for the difference was 0.04 in a test for a systematic effect (linear effect of group variable assumed) with a mean difference of 1.9 millimetre (95%, C.I. [0.1-3.7]). If treated as a non-ordered group variable, the mean difference between group 1 and 3 is estimated as -3.8 [95% C.I. -7.5,-0.1], p=0.04 and between group 1 and 2 estimated as 2.9 [95% C.I.-1.2,0.7] p=0.15.

Discussion

In this experiment, extra growth of the rabbit tibia on top of the normal growth was observed after combined tibial lengthening and the use of a femoral external fixator. The observed additional growth contradicts with most available literature, because in most instances, growth retardation occurs after limb lengthening as was seen in group 1 [5-10].

Several explanations are available for these observations. Compression forces on the growth plates of the knee may be responsible for growth retardation as in group 1 [7,10,11]. Decompression of the growth plate by arthrodiastasis may induce accelerated growth as seen in group 3 [3].

And as was shown in lambs, growth acceleration may occur after the application of a femoral external fixator only as in group 2 [12]. This effect could be similar to the temporary growth acceleration after a pediatric femoral fracture [16,17]. Growth acceleration may be caused by local hypervascularization which is observed after the trauma of lengthening and which may also be the explanation for growth acceleration after a pediatric femoral fracture [13]. Insulin-like Growth factor-1 (IGF-1) and Alkaline Phosphatase (AP) local release by bone trauma could also be an explanation of growth acceleration [14,15].
The hypothesis that unloading the growth plate may induce additional growth could not be proved, because extra growth was detected both in the study group with knee arthrodiastasis and in the group with a sham femoral fixator.
The intra-individual length measurements varied during the experiment, despite the use of a standardized measuring device. The variation is explained by the impossibility to position the rabbits very accurately. It was foreseen that this might happen. A statistical method to 'fade out' this inaccuracy is to use multiple sequential measurements in one individual during the experimental period. A consequence of variation in measurements is a larger standard variation of the individual measurements, which showed unreadable in a graph. The statistical analysis, as presented in figure 5b, was performed to show the relation of the effects between the groups.
Lengthening is a large intervention, which causes relative small biological growth effects after lengthening and joint distraction. It could not be expected that the growth would be increased by tens of percents, as we showed in a previous paper [3]. By presenting only the raw data of length discrepancy, the details may be lost in the general effect of lengthening. Any additional growth as anticipated would have been obscured by the effect of the lengthening without our model.
A subjective weakness of the study may be the small number in the groups. This is objectively contradicted by the statistical analysis in repeated measurements and the fact that growth was stimulated without exception in all subjects in experimental groups 2 and 3.
A true weakness of the study may be the fact that femur measurements could not be included in the study. Thus, the effects of tibial lengthening and the application of a femoral fixator with or without knee joint distraction on the whole limb were not analyzed.

The observed additional tibial growth in rabbits, that underwent tibial lengthening combined with either a sham femoral external fixator, or knee arthrodiastasis with a femoral external fixator, may have consequences for limb lengthening procedures in children treated with both tibial and femoral frames. The extent and the mechanisms of additional growth on the resultant limb length inequality remain unclear and need further studies.

Further investigations in this animal model may also provide information about the factors involved in bone growth or modified bone growth. The observed additional tibial growth was significant despite the small groups. Therefore, the described model may be useful for further research in the factors that influence bone growth.

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HJO initiated, designed, drafted and revised the study and manuscript, AJvD performed the radiographic and scintigraphic measurements, and collected the scintigraphic data, RB performed the statistical analysis of the data, drafted the graphs and the statistical section, WJAD, PMvR, AJV were associate investigators who were involved in study design, the experiments, and manuscript preparation.

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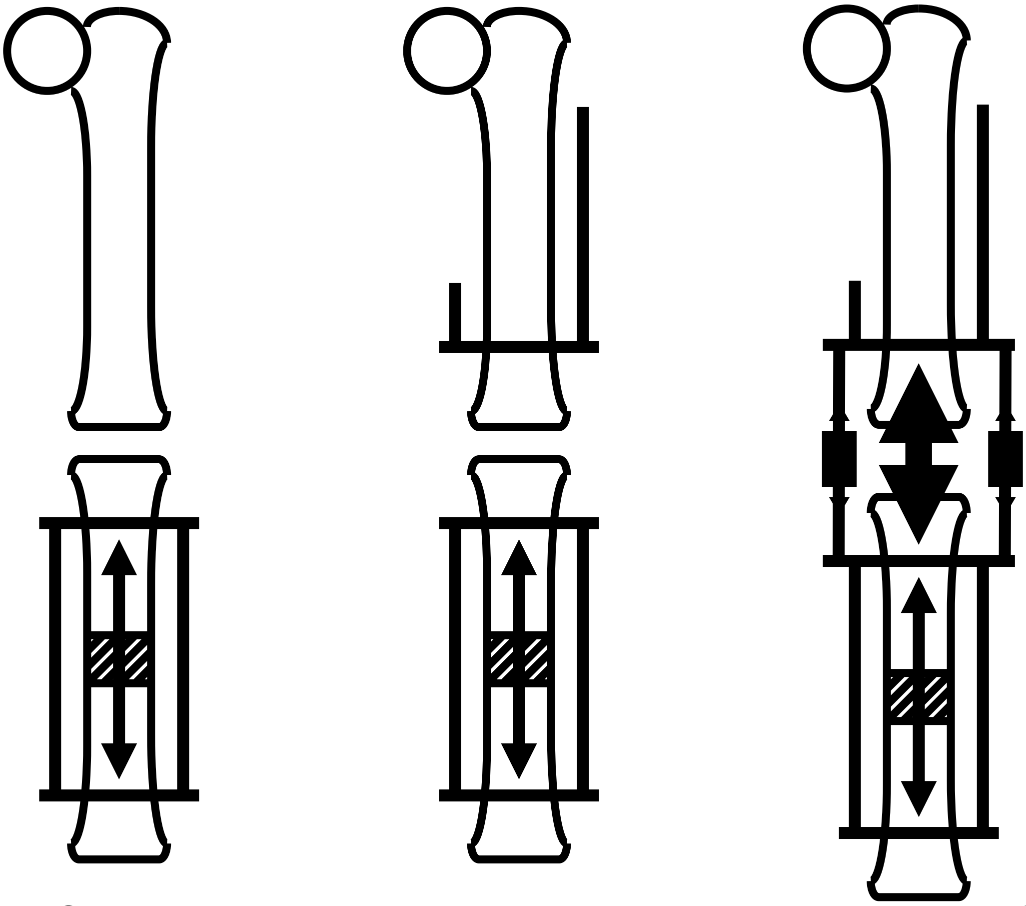
Figure 1. The specially designed 'rabbit' tibial lengthening and knee distraction device. Articulating distractors intend to bring reduced forces about the knee cartilage and growth plates.



Group 1 **Group**
2 **Group 3**

Figure 2. Schematical representation of the surgical and distraction procedures of the experimental groups. Group 1: tibial lengthening. Group 2: tibial lengthening and sham femoral external fixator (no knee distractors mounted). Group 3: tibial lengthening and femoral external fixator with articulated knee distractors.

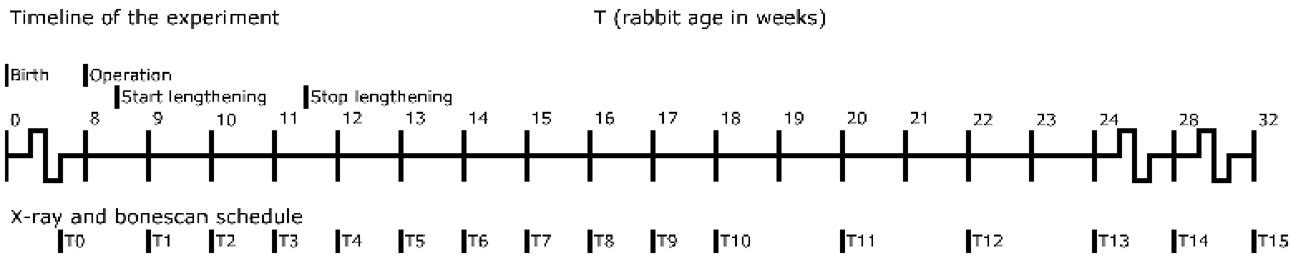


Figure 3. Timeline of the experiment. At several time intervals the length of both tibiae is measured . T0 is prior to the intervention/operation, T1 – T3 during lengthening, all other time points (T4 – T15) are at follow-up.

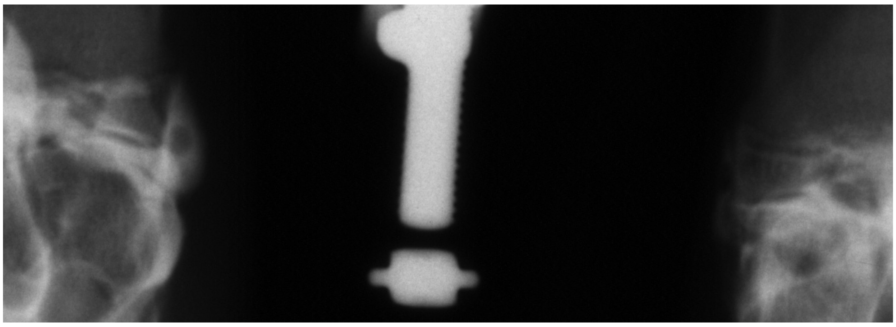


Figure 4. Knee distraction was checked with arthroradiography. In the left box, a thick contrast layer between the articular surfaces of the left femur and tibia indicates distraction of the knee joint, there is no contact between the knee cartilage surfaces. In the right box, a thin contrast layer indicates full contact of the femoral and tibial cartilage in the right knee.

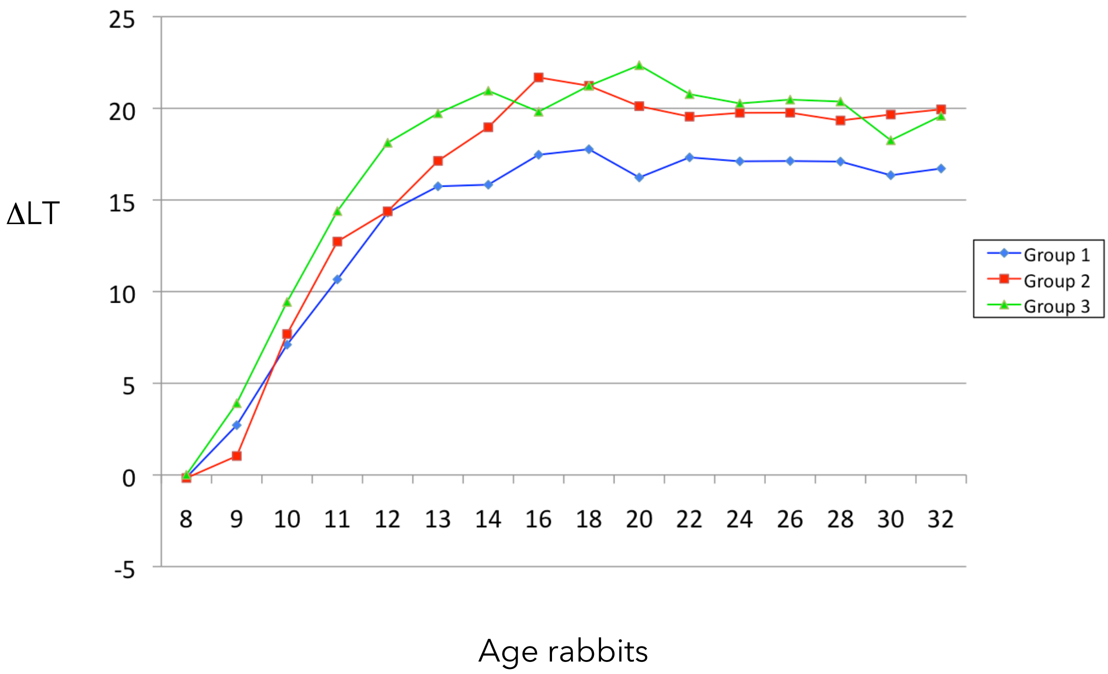


Figure 5A
Graphic representation of mean length discrepancy (ΔLT) between left and right tibia in millimeters on Y-axis, from age of the rabbits (X-axis) of 8 weeks in the experimental groups as described in the text. The first measurement is just prior to the initiation the experiment: the operation to apply the lengthening fixator (T = 8 weeks of age) and subsequent lengthening, which stopped after 3 weeks (T = 11 weeks of age) The first measurement after the lengthening is at T = 12 weeks of age.

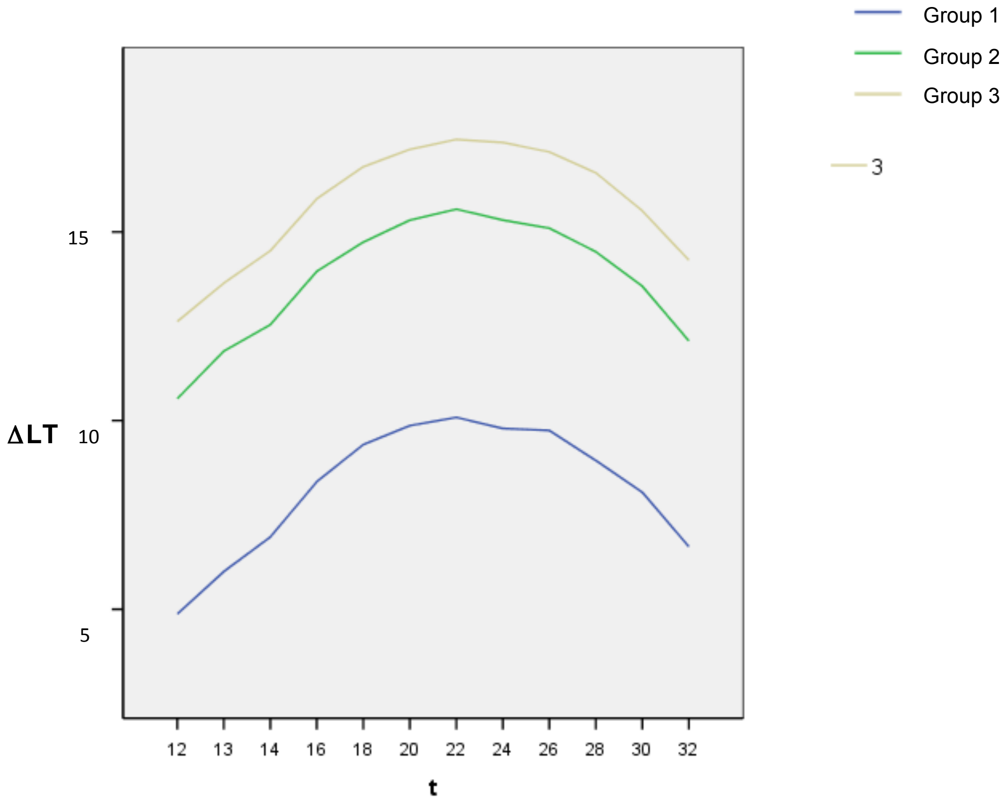


Figure 5B. A statistical model of the follow-up of limb length discrepancies. The graph shows the development of the length discrepancy in millimetres between the left and right tibia. The Y-axis represents de amount of length discrepancy between the lengthened left tibia and the control right tibia (ΔLT). The X-axis represents the age of the rabbits in weeks (t), the lengthening is stopped three weeks after the operation, for each group. Mean standard error for group-effect: 1.8 (95% CI can be approximated by [average +/- 3.6] for individual groups). The Trend-test for group effect: p=0.04

Chapter 5

Scintigraphic growth plate imaging in tibial lengthening in rabbits.

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Submitted

Abstract

Purpose Limited information exists about growth patterns of the paediatric limb after limb lengthening. Retrospective data from our clinic indicated that additional growth might occur after knee joint distraction during limb lengthening. In an experiment growth stimulation was observed during and after tibial lengthening and application of a femoral external fixator. Simultaneous measurement of the scintigraphic activity of the growth plates of the lengthened tibia compared to the contralateral tibia may reflect the growth speed of the tibia.

Methods A study with immature New Zealand white rabbits was designed to investigate the effects of tibial lengthening alone, combined with sham femoral external fixator and combined with knee joint arthrodiastasis on the tibial growth rate. Sequential quantative 99 Tc-HMDP (hydroxymethylenediphosphonate) scintigraphy of the proximal tibial growth plate was done to investigate whether growth speed and future growth could be deduced from scintigraphic growth plate activity in these study groups.

Results Scintigraphy of the proximal tibial growth plate showed a decreased growth plate activity after initiation of the lengthening in all lengthened tibiae.

Conclusions It was not possible to recognize a growth plate scntigraphic activity pattern that reflects the tibial growth observed in the study groups. Quantative scintigraphy of the growth plate is not a suitable technique to

follow up changes in osseous growth rate after interventions.

Introduction

Limb lengthening procedures are performed in children to equalize limb length discrepancy over 4 centimetres. Callus distraction with the Ilizarov circular external fixator is one of the available techniques to lengthen the femur and/or tibia. Although not widely used, simultaneous bridging of the knee joint and knee joint distraction (arthrodiastasis) is a recognized method for stabilization of instable joints during lengthening. Bridging is used for the treatment and prevention of joint contractures and for protection of the joint cartilage [1,2]. This technique is characterized by altered force transduction through the lower limb and enclosed growth plates, and by placement of pins in femur and tibia that transduce the distracting forces to the bone. In a group of 30 growing patients with more than 2 years follow up after a limb lengthening procedure, we found that additional growth occurred with bridging of the knee [3]. This extra growth may be related to the application of femoral frames and/or to exerted knee arthrodiastasis during lengthening. Arthrodiastasis may protect or even stimulate the growth plate [4].

An animal study was designed to investigate the hypothesis that arthrodiastasis of the knee during tibial lengthening causes additional growth in the tibia for a substantial period after the lengthening. Quantative ^{99}Tc-HMDP (hydroxymethylenediphosphonate) scintigraphy was used to test whether scintigraphy is a predictive tool for the growth pattern after limb lengthening, as has been shown in the growth rate in normal rabbits or after a fracture [5-7].

Materials and methods

Experimental design

After approval of the local institutional review board, nineteen 8-week-old New Zealand white rabbits were used in the experiment. An aluminium circular tibial and a semi-circular femoral external fixator with articulating knee distractors was developed for this study in our hospital by the Fine Mechanical Engineering Department (Figure 1). The external fixator was designed to allow at least 90° knee flexion. The study contained three groups (Figure 2), initially 5 in group 1, 7 each in groups 2 and 3. In group 1, only tibial lengthening was performed. In group 2, tibial lengthening was combined with the placement of a sham femoral external fixator without connection to the tibial fixator. In group 3, the femoral external fixator was coupled to the tibial lengthening device using the articulating knee joint distractors for arthrodiastasis. The lengthening procedure was started 3 days after the operation. The tibial external fixator was lengthened 20 millimetre (approximately 25% of the length at the start of the experiment) with daily increments of 1 millimetre. Lengthening over 25% may cause

growth inhibition [8]. Knee joint distraction in group 3 was done until an increased distance between femur and tibia was clearly recognizable on the radiographs. The distractions of the knee and the tibia could be performed without any need for sedation or pain relief. A day before the operation at the age of 8 weeks, and then at the age of 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32 weeks, a calibrated plain anterior-posterior radiograph of both tibiae and a ^{99}Tc-HMDP bone scintigraphy of the proximal tibial growth plate of both tibiae was made. In all, 1 pre-intervention and 15 follow up measurements were made. Prior to the radiographic and scintigraphic investigations, the rabbits were sedated. Tibial length was measured in millimetres on postero-anterior radiographs for which the rabbit was positioned in a specially designed device. A radiopaque ruler with 1 millimetre steps was incorporated in this device. All radiographs were scanned and digitalized. The tibia lengths were measured using the NIH Image 1.60 software package for Apple Macintosh with the radiopaque ruler as the reference.
The static scintigraphs of the growth plates were manually processed: an area of interest for each growth plate was drawn, and in this area three count samples were taken. The mean value of these samples was calculated. The proximal tibia growth plate scintigraphy counts on the left and the right side were compared within each rabbit at each measuring instance. A Q ratio between the left and right proximal tibia was calculated and used for statistical calculations.
The left/right ratio of the scintigraphic growth plate activity was correlated with the length discrepancy in time to investigate whether the scintigraphic growth plate activity is a reflection of the growth rate after limb lengthening. When the bone gap in the distraction zone is fully consolidated, the external fixator is removed. At the age of 32 weeks the rabbits are full grown and investigations were stopped.

Surgical procedures
All external fixators were placed on the left hind limb. The tibia was fixed to the frame with 2 crossed 1 mm Kirschner wires on each ring at the level of the proximal and distal metaphysis. The femur was fixed to the frame with 2 crossed 1 mm K-wires in the distal metaphysis on the semicircular ring and 1 lateral 2 mm half pin proximally in the trochanter region in the multiple hole block. The distracting knee articulator was placed just posterior to the anatomical flexion/extension axis of the knee. This placement resulted in further distraction when the rabbit tried to flex the knee (full flexion is the physiological rest position for a rabbit). Then, a tibial subperiosteal osteotomy was done in the mid-diaphyseal region. Pin placement and

fixation, position of the distraction articulator, osteotomy and knee distraction were controlled with fluoroscopy during the operation.

Statistical methods

Means, standard deviations, frequency tables and cross tabulations whenever appropriate give the basic description of the data. For the purpose of comparing the three groups of animals, a linear mixed model was used (SPSS version 11.0). For the analysis of relative length growth, the outcome variable was the length of the left tibia. Comparison of groups was restricted to time points above 11 weeks, after the lengthening procedure was stopped (“run-in” period).

For the assessment of scintigraphic activity of the growth plate, the ratio Q of the left to right PT was constructed as an outcome variable. First we analyzed the log(PT-right) as an outcome variable using the log(PT-left) as covariate, in strict analogy to the length-analysis. However, the results of that analysis were virtually identical to that of the (simplified) analysis where the ratio Q is directly used as an outcome variable (note that log(PT-right) minus log (PT-left) is indeed log(Q) by definition) so the simplification is actually that we verified that all significance tests gave the same results whether used on a log-scale or on the original one.

The model again is a random effects repeated measurements model with fixed time and group effects and random animal effects. The model predicts the (average) ratio Q as a function of time and subgroup. Only time points 3 weeks after initiation of the lengthening are taken into account. Finally, for prediction purposes, we computed the average ratio Q over all time points from week 3 up to week 8, per rabbit. This value, QMEAN, was then tested for predictive ability in predicting the left tibia length using time and the right tibia length as additional covariates. Again this was done in a mixed model. The test for additional predictive ability is the usual fixed-effect test of the mixed model.

Results

Three animals were euthanized within two weeks after surgery because of a femoral fracture in the left leg. One animal failing to thrive during the distraction period was euthanized also. All other animals thrived well after the operations with a normal increase of weight. So, 15 animals completed the experiment, 5 in group 1, 4 in group 2, and 6 in group 3. About 3 months after the operation the bone gap in the distraction zone was fully consolidated, and the external fixators could be removed.

The resulting difference in tibial length was visualized for each group as mean values in Figure 3. The measurements for each animal in time vary despite optimized circumstances. We tested the measurements from one

radiograph, this was consistent, but on a time curve rather large variations were noted in one animal from time point to time point. For this reason many measurements on a time scale were used to minimize this effect. Graphic representation of standard deviations would make a graph that could not be read, so only mean values were shown.
The raw data reveal that a gradual difference develops between the groups during lengthening and for a period after lengthening. These result in a small but measurable and statistical relevant difference between single tibial lengthening and the tibial lengthening procedures with a femoral external fixator, either sham fixator or femoral fixator for arthrodiastasis. The mean difference in tibial length increased 2.3 mm and 2.8 mm after the lengthening in groups 2 and 3 respectively as compared group 1, thus indicating extra growth as compared to single tibial lengthening.
In all rabbits, the proximal tibia growth plates of the treated legs showed less scintigraphic activity compared to the control leg during the whole growth period, starting at 3 weeks after the beginning of the experiment. Figure 4. The distraction zone of the tibia started to appear scintigraphically at 3 weeks after initiation of the lengthening procedure, at the same moment as the growth plate activity started to drop.
Differences in scintigraphic Q-ratio's between the three groups were not significant with a mean of 0.5 [95% C.I.-3.6,2.6], p=0.75).

Discussion

In this experiment, additional tibial growth was observed in all animals after combined tibial lengthening and the use of a femoral external fixator, either as a sham fixator or a fixator to exert knee arthrodiastasis. Additional growth is the extra growth that occurs on top of the growth that was measured after single tibial lengthening.
The study setup was made to investigate the effect of joint distraction on growth after lengthening [3]. Since a joint distraction is at least a double intervention; attachment of a femoral fixator and joint distraction, we decided to use two experimental groups: a sham femoral fixator and a femoral fixator for joint distraction. We had to anticipate that the sole application of a femoral fixator could induce additional growth as well. No statistical distinction could be made between the effect of a sham femoral external fixator and knee arthrodiastasis applied during tibial lengthening. Details are available in a previous report [9].
Several reports suggested the value of scintigraphic activity in the growth plate as the biologic exponent of growth plate activity [5-7], but no data exist about the value of scintigraphy after limb lengthening. In this study, scintigraphic activity of the growth plates of the tibia was measured and varied considerably between individuals during the experiment, but was

decreased in all rabbits after initiation of the lengthening. No differences could be observed between the study groups. Since scintigraphic activity is the visualization of the mineralisation process of bone, decreased scintigraphic activity in the growth plates is the reflection of decreased bone formation. The external fixator may have been too cumbersome for the rabbits to load the leg normally, resulting in decreased bone formation by disuse. In this study setup it was not possible to show any relation between bone growth and scintigraphic growth plate activity, in contrast to other studies, albeit the latter studies have a different study setup [5-7].

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HJO initiated, designed, drafted and revised the study and manuscript, AJvD performed the radiographic and scintigraphic measurements, and collected the scintigraphic data, RB performed the statistical analysis of the data, drafted the graphs and the statistical section, WJAD, PMvR, AJV were associate investigators who were involved in study design, the experiments, and manuscript preparation.

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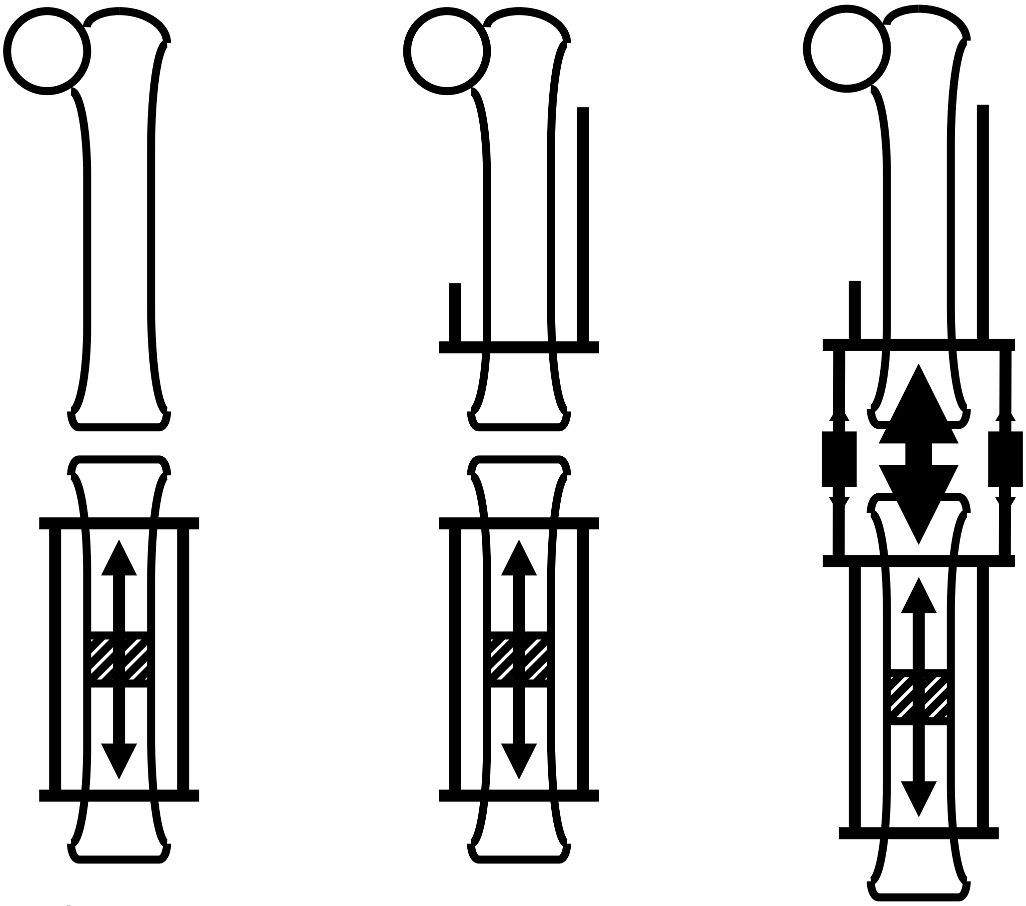
Figure 1. The specially designed 'rabbit' tibial lengthening and knee distraction device. Articulating distractors intend to bring reduced forces about the knee cartilage and growth plates.



Group 1
Group
2
Group 3

Figure 2. Schematical representation of the surgical and distraction procedures of the experimental groups. Group 1: tibial lengthening. Group 2: tibial lengthening and sham femoral external fixator (no knee distractors mounted). Group 3: tibial lengthening and knee distraction with femoral external fixator and articulated knee distractors.

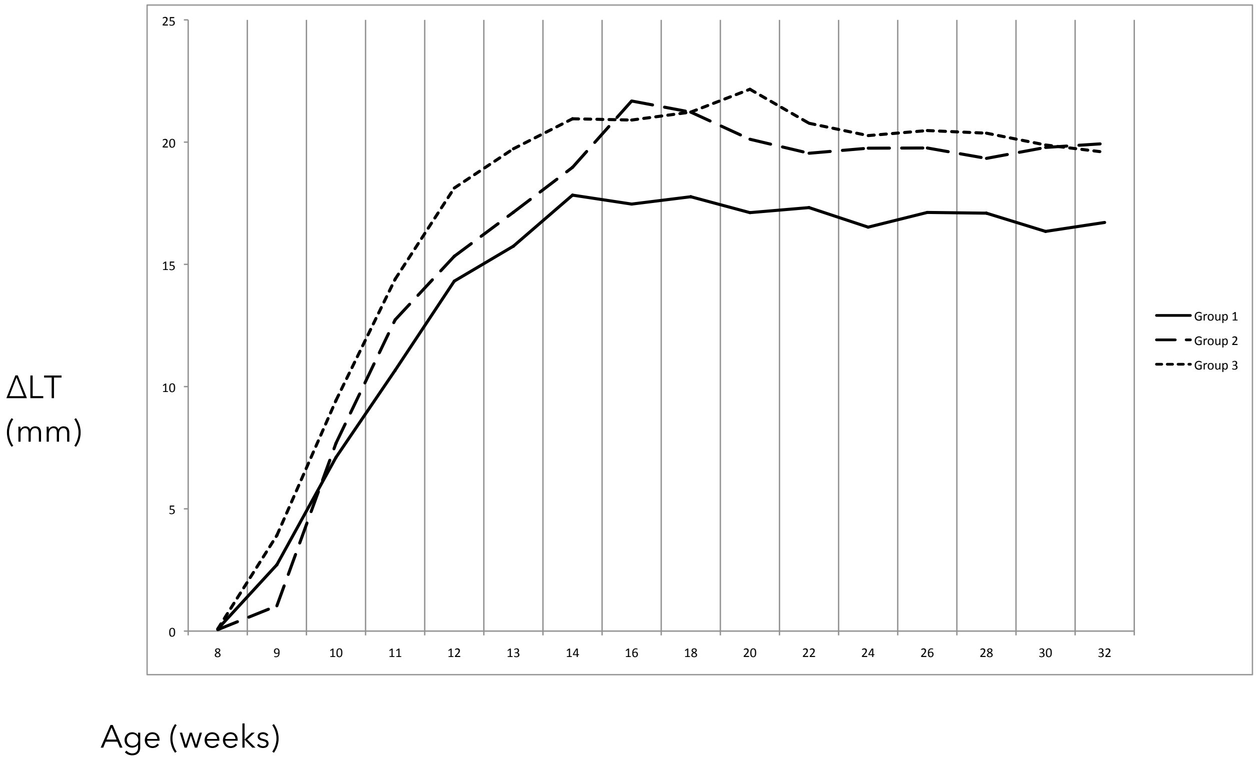


Figure 3. The Figure represents the actual means of the limb length discrepancy in the 3 groups. The y-axis represents the tibial length discrepancy in millimeters (Δ LT). The x-axis represents the age of the rabbits. The experiment starts at age 8 weeks and ends at 32 weeks, at maturity. On the x-axis all points of data collection are represented with an age value.

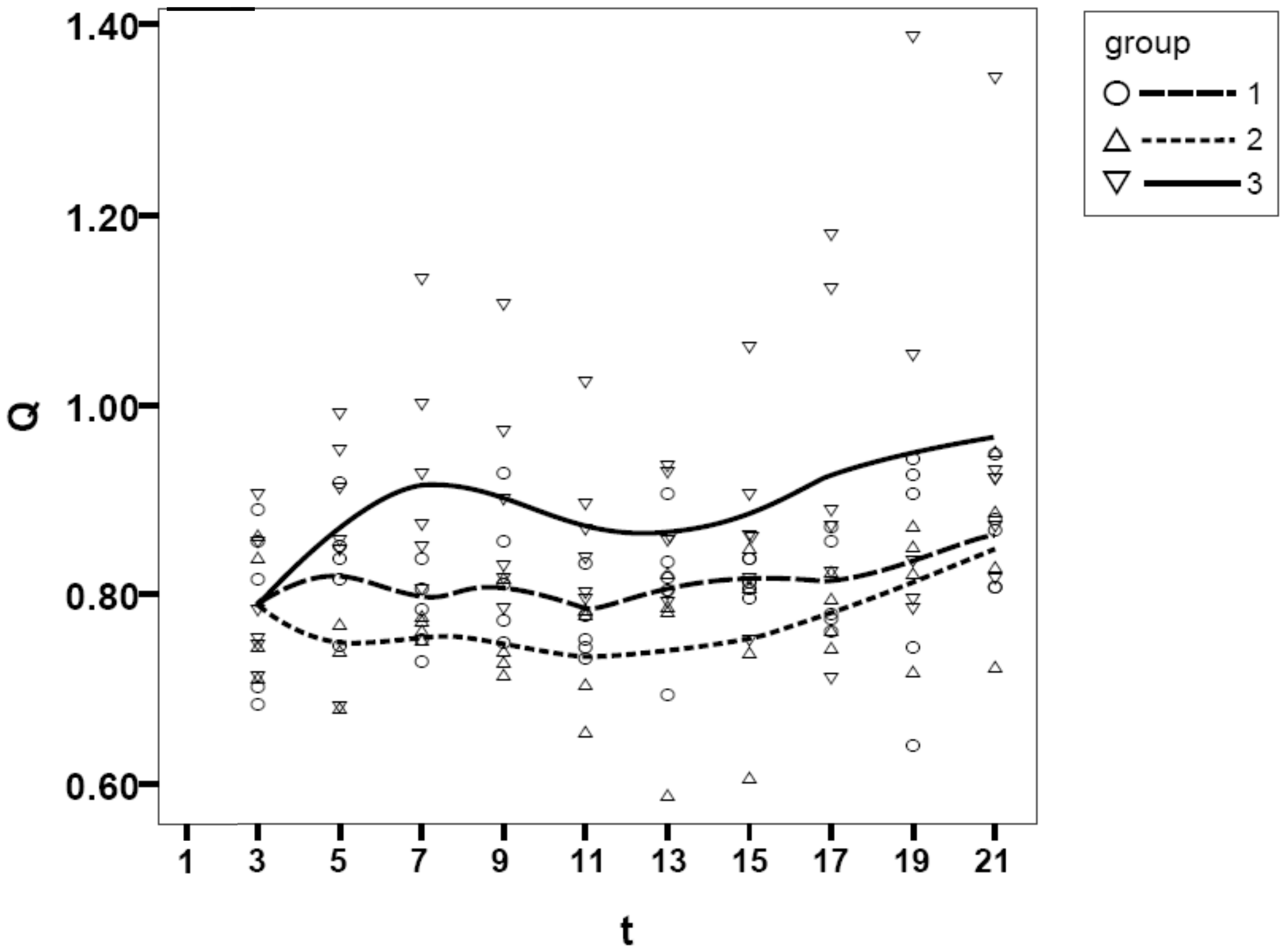


Figure 4. This graph shows the development of the left/right ratio ^{99}MDP-Tc activity of the proximal tibial growth plate during the experiment. The number on the y-axis represents the ratio of the scintigraphic activity between the left and right proximal tibial growth plate. A left/right ratio less than 1 means that the left physis has less scintigraphic activity than the right physis. The left tibia has been lengthened. The x-axis represents the time in weeks after initiation of the lengthening. The lines in the graph represent the mean values for each group. The three circular and triangular symbols are the values for each individual at each time point. No statistical relations between the groups could be identified.

Chapter 6

Lower limb deformity due to failed trauma treatment corrected with the Ilizarov technique.

Factors affecting the complication rate in 52 patients.

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Abstract

Background and purpose Failed treatment of fractures may be corrected by the Ilizarov technique but complications are common. In 52 patients with compromised healing of femoral and tibial fractures, the results of secondary reconstruction with Ilizarov treatment were investigated retrospectively in order to identify the factors that contribute to the risk of complications.
Methods A consecutive group of 52 patients was analyzed. The median interval between injury and secondary reconstruction was 3 (0.1-27) years. The patients had failed fracture treatment resulting in bone defects, pseudarthrosis, infection, limb length discrepancy (LLD), caused by bone consolidation after bone loss, malunion, soft-tissue loss, and stiff joints. Most patients had a combination of these deformities. The results were analyzed by using logistic regression in a Polytomous Universal Mode (PLUM) logistic regression model.
Results The median treatment time was 9 (4-30) months, and the obstacle and complication rate was 105% per corrected bone segment. In 2 patients treatment failed, which resulted in amputation. In all other patients healing of nonunion could be established, malunion could be corrected, and infections were successfully treated. The statistical analysis revealed that relative bone loss of the affected bone was the only predictor for occurrence of complications. From these data we constructed a simple

graph that shows the relation between relative bone loss of the affected bone and risk for complications.
Interpretation Relative bone loss of the affected bone segment is the main predictor of the complications after Ilizarov treatment of previously failed fracture treatment. The visualization of the analysis in a simple graph may assist to compare the complication rates in literature.

Introduction

Treatment of the traumatized lower limb rarely fails [1-4]. High failure rates are only seen in the most severe types of injury, such as open fractures Gustilo type 3B and 3C. This type of injury frequently ends up with severe deformities [5, 6]. The Ilizarov method may be helpful in treating these post-traumatic deformities including malalignment, non-union, bone defects, limb length inequality and osteomyelitis.
The indication for Ilizarov treatment remains limited to the more severe types of injury, as the complication rate during treatment is high and the learning curve is notoriously long [7]. For the latter reason, it is not easy for surgeons to achieve adequate experience using the Ilizarov method when treating such post-traumatic pathology.
Choosing the Ilizarov method has severe consequences for patients. Disturbance of daily life by the bulky frame, muscle impalement by transfixing wires with associated loss of joint motion, pin-track infections and pain, may all cause great discomfort and psycho-social problems [8]. The decision to treat with the Ilizarov method must therefore be made after a careful analysis of existing deformities [9, 10], and sound patient selection with realistic treatment goals; sometimes, it is necessary to accept residual shortening, a stiff joint, or other deformity.
We conducted a retrospective study to evaluate the outcome of Ilizarov reconstruction treatment of post-traumatic lower limb deformities in our clinic.
In order to understand the achieved outcome, we investigated the statistical relationship between several variables of the deformities and the complication rate.

Patients and methods

Patients

A retrospective study was performed in 52 patients (33 men) with malunion and nonunion after lower limb trauma. The median age at the start of the Ilizarov treatment was 27 (6-82) years. The median interval between injury and secondary reconstruction was 3 (0.1-27) years (Table 1).
In these 52 patients, 54 corrective procedures in 56 deformed bone segments were done. This means that in one patient (patient 1) the

deformity was corrected in 2 sequential procedures, in one patient (patient 42) 2 limbs were corrected at the same time, and in 2 patients (14 and 27) femur and tibia were corrected in the same procedure.
All patients but one (patient 21) had initially been treated in other hospitals. 26 procedures were planned for malunited and 28 for nonunited fractures. Shortening, angulation and rotational deformity were considered as malunions. Nonunions were deformities with bone defects, or fractures with bone contact that did not unite. 19 non-unions were infected. A median shortening of 4 (1.5-8) cm or 9 (4-21)% shortening of the affected bone was found in 25 patients and a bone defect of 8.5 (2-15) cm or 18 (4-29)% of the affected bone was found in 18 patients.

Methods

Deformities were classified according to Dahl et al. [7].
The Ilizarov procedure was aimed to restore bone continuity, mechanical axis, limb length, and -if applicable- to heal osteomyelitis. When complete correction was not envisaged, a calculated residual deformity was accepted. In these patients, the residual deformity was not calculated as a complication. This strategy was implemented for 5 patients. In patient 1, a two-stage treatment was planned because of a bone defect of 13 cm. Patient 19 had an intra-articular distal femoral fracture with a bone defect of 3 cm. Pre-existent damage to the peri- and intra-articular tissues resulted in a functional knee arthrodesis, which was judged not to improve by bone union. Since a knee arthrodesis requires a limb shortening of 1.5-2 cm, limb lengthening makes no sense. Patient 31 had a 13 cm bone defect that had existed for 15 years. As he was suffering from AIDS, no attempt was made to correct the shortening. The treatment goal in this patient was restoration of bone continuity permitting the patient to walk with the help of an orthosis. Patients 29 and 39 had a severe alcohol abuse problem. Thus, the decision was made to treat the bone deformity only, and accept the limb shortening.
All patients were treated with a classical circular frame with Ilizarov rings. Bone fixation was performed by using half pins and tensioned transfixation Kirschner-wires. The bone was divided by a multiple-drill hole subperiosteal corticotomy. All lengthenings and corrections were monofocal.
Nonunions and bone defects were treated with trimming and compression of bone ends [11, 12]. In some patients, additional surgical procedures were planned during or after application of the Ilizarov frame.
In treating osteomyelitis, antibiotics were chosen according to culture sensitivity. The duration of the antibiotics treatment was at least 6 weeks.
After removal of the Ilizarov frame, the patients were referred to physiotherapy for further rehabilitation and they were followed up until a

stable end situation was reached. was not evaluated, Joint mobility was evaluated at the normal follow-up visits, but not muscle strength.

Evaluation

Complications of surgical correction were classified according to [13]. We added an extra category to this classification; psychosocial dysfunction, including intoxication states and non-compliant behaviour to treatment [8]. This complication may increase the risk of other complications and may change or may lead to premature cessation of the treatment.

Statistics

Major determinants of the deformities such as large relative bone loss of the affected bone, either shortening or a bone defect, malunion, (infected) non-union would be suspected to affect treatment outcome negatively. Other co-existing deformities could influence the outcome as well, and were grouped in a classification as described by Dahl et al.[7]. To assess the relationship between these factors and the complication rate, a Polytomous Universal Mode (PLUM) logistic regression approach was used. Instead of modelling the probability of “complication” as a dichotomy, this approach models the probability of more than 2 ordered outcome categories simultaneously. The independent variables were all added to the model, and then in a backwards stepwise way the multivariate insignificant predictors were removed (relative bone loss, malunion, nonunion and severity of deformity by the Dahl classification [7]).
The outcome variable was the count of the number of complications and the model estimated the probability of observing 0, 1, 2 or 3 complications as a function of the independent predictors.

Results

The median external fixator time was 9 (3-30) months. The median amount of lengthening was 3.8 (0.5 – 15) cm. The median healing index was 2.3 (0.9 – 9.0) months per cm of lengthening (Table 2).
The defined treatment goal was achieved in 50 patients. Patient 11 could not tolerate the long duration of the treatment. An above-the-knee amputation was done. Due to severe pulmonary disease, further treatment could not be tolerated in patient 49, and a below-the-knee amputation was performed.
14 patients had pin tracts infections, these are not considered as complications according to Paley et al.[13]. The treatment led to 27 obstacles and 32 real complications, producing a total complication rate of 105% per treated bone segment.

Probability of complications

In our study the minimum number of complications in one patient is 0 and the maximum 3. The relative amount of bone loss of the affected bone was 4 - 29%. The statistical analysis showed that relative bone loss, i.e. percentage bone loss of the affected bone, was the single most important statistical determinant for complications. The difference of the coefficient of the main predictor "bone loss" between the polytomous analysis and the univariate analysis was small: the coefficient was going up from 0.083 to 0.091 by introducing the residual confounding due to not taking into account the other parameters. Thus, the simpler univariate model was chosen to show the magnitude where, given a specific bone loss percentage, the probabilities of 0, 1, 2, or 3 complications are estimated as an ordered outcome variable. The outcome of this model is visualized as a graph (Figure). It shows the probability of encountering a specific number of complications in relation to the relative amount of bone loss. The standard errors of the estimates that play a role in generating the graph are shown in Table 3. The usual underlying confidence intervals are in Table 3 and not in the graph because the focus of the graph is not on regression lines, but on boundaries (thresholds) between the occurrences of a specific number of complications.

The easiest way to interpret this graph is as follows. Imagine a vertical line at a specific percentage of bone loss say 8%. That line cuts through the boundary between the area of 0 and 1 complications, at precisely 50%. That implies that 50% of the patients with a bone loss of 8% will experience 0 complications (and hence 50% will experience 1 or more complications). Likewise a vertical line at 18% bone loss will cut the boundary between the area marked as '1' and '2' at 50%; hence, with such a bone loss, 50% of the patients will have at most 1 complication and 50% will have 2 or more complications. At the very end of the graph, the bone loss is assumed to be 29%, the maximum observed in our study. At this point the probability of experiencing 3 or more complications is 34%, hence 66% of the patients with such a bone loss, will have up to 2 complications.

The graph can also be read off horizontally: a horizontal line at 50% complication risk cuts the boundaries at 8% (the 95% CI for this estimate is 0 - 18%) and 18% (95% CI 7 - 29%).

Discussion

In this study of secondary reconstruction for post-traumatic deformities, the treatment goal could be achieved in 50 out of 52 patients. In 5 of these 50 patients the limb length inequality was intentionally undercorrected – because of patient factors. These patients had problems that should be addressed by limb reconstruction, but at the same time they had problems that would be a contraindication for limb reconstruction, such as AIDS, severe alcohol abuse and severe behavioural or psychiatric disorders. Sometimes combined soft tissue, bone, and joint problems cannot all be solved by limb reconstruction or any other treatment. The main goal for these patients should be a stable leg to stand on, without pain, and fit for the application of an orthosis to compensate for the residual deformity. Adapted treatment goals indicated by concomitant deformities or conditions have rarely been reported [14, 15]. There must be an under-reporting, because it is unlikely that this type of patient is not represented in other reconstruction centres. It is undesirable not to report on these patients, because the limitations of treatment or realistic treatment goals of limb reconstruction must be made clear in order not to harm the patient unnecessarily.

In our study, soft tissue problems such as joint contracture or muscle loss could not or could only be partially solved, which corresponds to other reports in the literature [15-19]. Swiontkowski et al. concluded that soft tissue conditions were prime determinants for reconstruction or amputation of severely traumatized limbs, so it is difficult to understand why the soft tissue condition as a limitation for treatment outcome is hardly reported [20].

The treatment resulted in 59 "obstacles" and "real complications", which is a complication rate of 105% for 56 treated bone segments. This rate is similar to the results reported for limb reconstruction after failed trauma treatment (ranging from 57 to 232%) [12, 15-17, 21-27]. However, the variety in patient groups is large, making comparison of results in the literature difficult. The value of complication rates is limited unless the deformities are classified. To make comparison of treatment outcomes easier, Dahl et al. introduced a classification of the severity of deformity [7].

Evaluation of our patient group with logistic regression analysis in a PLUM logistic regression model revealed that neither the severity classification nor the type of the deformity (malunion or (infected) nonunion) was related to the risk of complications. The percentage or proportionate bone loss of the affected bone was the only significant statistical factor that we could identify for the risk of complications. Resultant graphic representations of such analyses could also be constructed by other investigators, which make comparison between authors possible.

When we break down the complications, the (re)fracture rate was 5 in 56 treated bone segments (9%), which is similar to O'Carrigan et al. [28] in a report of 986 lengthenings (8%). Also, all other local types of complications in our series were similar to those in most of the relevant literature [29].

Psychological analysis and social support play an important role in patient selection and treatment [12, 15, 17]. Patients who are well prepared for the treatment and do not have major psychological problems have better results [8]. The mental and physical discomforts usually resolve after treatment [8, 30, 31]. Mental condition is important in sustenance of the treatment, which was illustrated in the failure or severe complications in 2 patients and adapted treatment goals in 5 patients in our series.

Beside the type of deformity, the complication rate of the Ilizarov treatment is notoriously influenced by many other factors. It is known that surgeon's experience of over 30 procedures is needed to overcome the learning curve problems [7]. This was not an issue in this study. Smoking was not evaluated as a determinant, because we had no information.

In conclusion, our study shows that the Ilizarov method is a valuable tool in treating severe types of bone loss and limb deformity with or without active infections. Reconstructive surgery using the Ilizarov method should always be considered as a treatment modality when amputation is imminent, though it is still difficult to judge when this type of reconstructive surgery is indicated [32]. Our analysis shows that the relative amount of bone loss from the affected bone or the relative amount of bone to be reconstructed dictates the complication rate. This is represented in a graph, which may be helpful for comparisons with published material involving similar reconstruction procedures.

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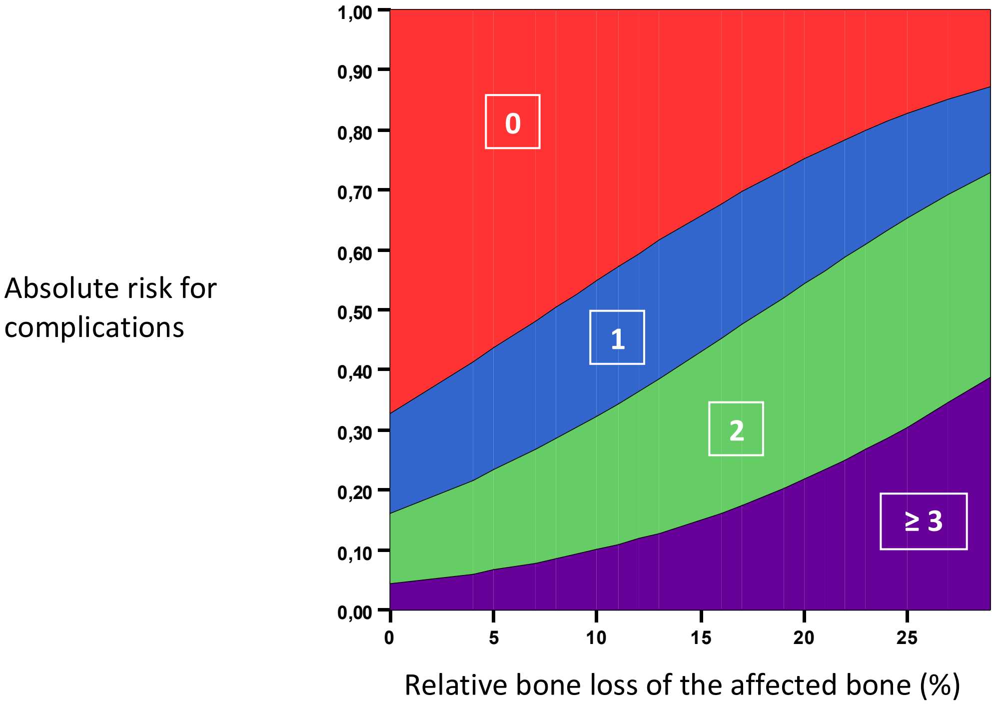

Figure. Population estimates of the relation between the percentage bone loss and number of complications in a univariate logistic regression model. The standard errors of the estimates that play a role in the picture, are represented in Table 3. The y-axis represents the estimated risk for the amount of complications at a certain relative bone loss of the affected bone (%) as represented on the x-axis. For example: the risk for 1 or more complications is 50% in a bone loss of the affected bone of 8%.

Table 1. Pre-operative patient data

Procedure	Patient	Sex	Age	Cause	Tibia	Femur	Interval Rx (months)	Deformity type	Concomitant Factors	Pre-Rx (n)	LLD (cm)	Defect (cm)	Percent (%)	Angular/Rotation deformity (°)	Dahl
1	1	male	17	traffic	L		5	infected defect pseudarthrosis		2		13	24		4
2	2	male	34	traffic	R		65	LLD/malunion		2	5		12	25 varus	2
3	3	female	22	home	L		42	LLD		2	4		9		2
4	4	female	39	traffic	R		81	LLD		>5	4,5		13		2
5	5	male	28	traffic	R		176	LLD/malunion		2	4		8	40 varus/recurvatum	2
6	6	female	32	traffic	L		141	LLD/malunion		1	3,5		10	40 varus/recurvatum	2
7	7	male	16	traffic		R	74	LLD		1	4		8		1
8	8	male	22	traffic		L	11	defect pseudarthrosis		4	2		15	29	5
9	9	male	24	planecrash		R	2	infected defect pseudarthrosis		2		9	22		4
10	10	female	22	traffic		L	31	LLD/malunion		4	>5	5	10	30 internal rotation	3
11	11	male	23	traffic		L	10	infected defect pseudarthrosis		1		12	25		4
12	12	female	21	traffic		L	42	LLD/malunion	6, 8	>5	8		21	20 varus	5
13	1	male	21	traffic		L	43	LLD/malunion			4,5		11	30 varus/recurvatum	3
14	13	male	18	home	R		38	LLD		1	5		10		1
15	14	male	29	job	L	L	12	LLD/malunion		1	5		12	35 varus	3
16	15	male	27	job		R	18	LLD/malunion		1	5		13	40 varus/recurvatum	2
17	16	female	63	traffic	R		56	pseudarthrosis		2				15 valgus	2
18	17	female	30	traffic	R		14	defect pseudarthrosis		>5		8	20		3
19	18	male	17	war		L	24	infected defect pseudarthrosis	7	2		9	19		4
20	19	male	43	traffic	L		1	defect pseudarthrosis				3	7		2
21	20	male	34	traffic	R		325	malunion		>5	3		7	15 valgus	2
22	21	female	21	traffic	R		52	LLD		1	3		7		1
23	22	male	21	traffic	R		44	infected defect pseudarthrosis		>5		8	21		4
24	23	female	82	home	L		25	infected pseudarthrosis	13	1	2		5		2
25	24	male	18	sport	R		46	LLD/malunion			2		5	30 varus/recurvatum	1
26	25	male	24	traffic	L		83	infected malunion		2				15 varus	3
27	26	female	44	sport	R		8	infected pseudarthrosis		1	2		5	20 varus	3

Table 1. Pre-operative patient data (continued)

Procedure	Patient	Sex	Age	Cause	Tibia	Femur	Interval Rx (months)	Deformity type	Concomitant Factors	Pre-Rx (n)	LLD (cm)	Defect (cm)	Percent (%)	Angular/Rotation deformity (°)	Dahl
28	27	male	37	traffic	L	L	108	LLD/malunion	6	3	1,5		4	30 valgus	4
29	28	male	40	traffic	L		17	infected defect pseudarthrosis	9	>5		6	14		4
30	29	female	50	traffic	R		1	infected defect pseudarthrosis	12	1		5	13		2
31	30	male	17	traffic		L	38	LLD/malunion		1	2		4	20valgus	2
32	31	male	36	war		R	180	infected defect pseudarthrosis	11	2		13	27		4
33	32	female	40	traffic	L		13	infected pseudarthrosis		3				10 varus	4
34	33	female	44	traffic	R		75	LLD/malunion	4, 6	1	3		8	45 varus/recurvatum	3
35	34	male	47	traffic	L		324	malunion		1	2		5	15 varus	1
36	35	male	17	traffic	L		4	infected defect pseudarthrosis		4		9	22		3
37	36	male	17	home		L	41	malunion			4		8	25 valgus/recurvatum	2
38	37	female	27	traffic	L		6	infected pseudarthrosis	2	>5					3
39	38	male	40	job	R		189	malunion tibia & pseudarthrosis ankle		2	2		5	30 valgus	4
40	39	female	51	sport		R	21	infected defect pseudarthrosis	9	>5		6	13		3
41	40	male	27	war	R		28	LLD/malunion		2	2		5	20 valgus	2
42	41	female	36	traffic		R	198	LLD/malunion	6, 12	3	2,5		5	10 varus	3
43	42	female	21	traffic	R		13	infected pseudarthrosis	3, 5	1					4
44	42	female	21	traffic	L		13	pseudarthrosis	3, 5	2					4
45	43	male	25	traffic	R		8	defect pseudarthrosis		1		10	24		3
46	44	male	37	war	L		96	infected defect pseudarthrosis		3		4	10	15 varus	3
47	45	male	32	traffic	L		50	malunion	3	4				30 valgus	3
48	46	female	29	traffic	L		57	malunion		1				15 varus	1
49	47	male	17	traffic		L	1	infected defect pseudarthrosis		2		12	23		4
50	48	male	17	traffic	L		4	infected pseudarthrosis		1					2
51	49	female	60	traffic	L		14	infected defect pseudarthrosis	1, 2	2		3	8		4
52	50	male	23	traffic		R	2	defect pseudarthrosis		1		2	4		2
53	51	male	48	traffic	R		36	pseudarthrosis	9, 10					30 valgus	2
54	52	male	17	traffic	R		60	LLD		2	4,5		13	23 recurvatum	2

Table 1. Legend

Interval Rx: Interval between trauma and correction of the deformity with the Ilizarov device.

Concomitant Factors: Concomitant factors influencing the severity of the deformity according to Dahl (1994); 1 intra-articular fracture; 2 compartment syndrome; 3 skin contracture caused by burns; 4 knee flexion contracture (degrees), and/or joint stiffness; 5 equinus deformity (degrees), and/or joint stiffness; 6 ligamentous instability knee; 7 ischiadical nerve lesion; 8 failed lengthening; 9 alcohol abuse; 10 liver cirrhosis; 11 AIDS; 12 soft tissue defect; 13 severe osteoporosis.

Pre-Rx: Amount of operations for correction of the deformity before initiation of the Ilizarov treatment.

LLD: Limb length discrepancy in centimetre, amount of bone loss with united fracture.

Defect: Amount of bone loss in centimetre due to the trauma, there is no union nor contact between the bone ends.

Percentage: Proportionate amount of bone loss of the affected bone in percentage compared to the length of the uninjured bone.

Dahl: Grading of the deformity according to the classification of Dahl et al. (1994) [7].

Table 2. Results

Procedure	Patient	Tibia	Femur	Post angulation (°)	rLLD cm	Rx in frame	Rx after Ilizarov	Obstacles & complications obstacles	real complications
1	1		L		4,5	2, 4	4	7	6, 9
2	2	R					13		8, 10
3	3		L			4	11	7, 10	
4	4	R							
5	5		R	50 varus/procurvatum			6, 11	10	3, 11
6	6	L							
7	7		R				14		10
8	8		L				14		8
9	9	R				1, 6, 7		7, 8, 10	
10	10		L			8	14	7	9, 9
11	11		L				9		11
12	12		L		2	6	11, 15	8	10
13	1		L		1		11	8	10
14	13	R			1				
15	14	L	L				11		10
16	15		R						
17	16	R							
18	17	R				4	5, 13	7	7, 11
19	18		L						
20	19	L			3	3, 6		8, 8, 10	3
21	20	R				4			
22	21	R							
23	22	R		15 recurvatum	1			3, 8	
24	23	L							
25	24	R			2				
26	25	L			1		1, 3		8, 10
27	26	R			2	9			

Table 2. Results (continued)									
Procedure	Patient	Tibia	Femur	Post angulation (°)	rLLD cm	Rx in frame	Rx after Ilizarov	Obstacles & complications	
								obstacles	real complications
28	27	L	L			4	8, 11, 12		
29	28	L				10	2		9
30	29	R			6		16		9
31	30		L						
32	31		R		13	4			7
33	32	L							
34	33	R			2				
35	34	L						8	
36	35	L						3	10
37	36		L		1				
38	37	L				4	5		7
39	38	R			1,5				
40	39		R		7	6		7	11
41	40	R		10 valgus		10			3
42	41		R				11, 14, 15		10
43	42	R					1, 1		8
44	42	L					11	3	10
45	43	R				4	6	10	3
46	44	L			2				
47	45	L				6	1, 1	7, 8	8
48	46	R				5, 6		8	
49	47		L			2, 4, 6	4, 5, 7	6, 8	7
50	48	L							
51	49	L				4	10	8	7, 8
52	50		R		2				
53	51	R							
54	52	R							

Table 2. Legend

Post angulation: Bone angulation after lengthening procedure in degrees

rLLD: Residual limb length discrepancy in centimetre after the corrective procedure.

OR in frame: Operations while the Ilizarov frame was worn; 1 fibula osteotomy, 2 recorticotomy, 3 fasciotomy, 4 autologous bone graft, 5 débridement pin tract, 6 adjustment frame, 7 contractures release/lengthening tendon, 8 patella distraction with Ilizarov, 9 débridement of the deformity site, 10 free muscle flap.

OR after Ilizarov: Operations after the Ilizarov frame was removed; 1 débridement, 2 open reduction/internal fixation for refracture or delayed consolidation, 3 intra-medullary nail after refracture, 4 external fixation after refracture, 5 autologous bone graft, 6 correction osteotomy, 7 vascularized free fibular graft, 8 total knee arthroplasty (TKA), 9 above knee amputation, 10 below knee amputation, 11 closed arthrolysis knee, 12 treatment infected TKA, 13 release toe flexors and Achilles tendon lengthening, 14 VY-lengthening quadriceps tendon, 15 anterior cruciate ligament reconstruction, 16 re-Ilizarov fixation.

Obstacles & Complications: Paley obstacles and complications [13]; 1 muscle contracture, 2 joint luxation, 3 axial deviation (minor <5°, major >5°), length inequality >2cm, 4 neurological injury (peroneal nerve), 5 vascular injury (or compartment syndrome), 6 premature consolidation, failure to reach equality, 7 delayed consolidation, 8 pin-site problems, infections, 9 fracture, 10 joint stiffness, 11 alcohol/drug addiction, psychosocial dysfunction

		Estimate	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Threshold	[n complications = 0]	.712	.474		-.218	1.641
	[n complications = 1]	1.648	.518		.632	2.663
	[n complications = 2]	3.099	.650		1.825	4.374
Location	Relative bone loss	.091	.036	.011	.021	.161

Table 3. Population estimates of the relation between relative bone loss of the affected bone and the number of complications, based on a univariate model. This shows the standard errors of the estimates that play a role in generating the accompanying graph (see figure)

Chapter 7

Arthrodesis of the knee after an infected arthroplasty using the Ilizarov method

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Abstract
We treated 15 patients by arthrodesis of the knee after removal of an infected total knee arthroplasty, using an Ilizarov ring fixator. Eight had a failed arthrodesis by another technique. The mean age of the patients was 75 years, the mean duration of retention of the frame was 28 weeks, the mean treatment time 51 weeks, and the mean follow-up 52 months. All but one knee fused at the first attempt, a rate of union of 93%. The incidence of complications related to treatment was 80%. The length of treatment and rates of complication were attributed to advanced age and the adverse local clinical factors in these patients. The Ilizarov method is a promising technique for achieving arthrodesis under these circumstances.

Introduction
The reported incidence of infection in total knee arthroplasty (TKA) varies from 0.57% to 15% [1-13]. Risk factors for infection are rheumatoid arthritis [1,4], the chronic use of corticosteroids [5,8-10], diabetes mellitus [11], poor nutrition, obesity, old age, prolonged hospitalization [9], previous knee surgery [4,5,10], deep infection [1,12] before implantation, the use of hinged prostheses [1,4,6,10] complications of wound healing after implantation [1,4,6,13] distant infection, and skin lesions [6].
Arthrodesis after a knee prosthesis has become infected may be required when there is much loss of bone, when the extensor function of the knee is deficient, with the soft tissues around the knee compromised and with very little movement of the joint [14-19]. In the past, various techniques have been used to achieve arthrodesis, with rates of union ranging from 29% to 100% [1,4,7,8,14,16,17,20-30]. Single-plane external fixation is the least successful technique (29% union) [9], and intramedullary nailing the best with fusion in 88% to 100% [24,26,29,30]. An intramedullary nail, however, should only be used after the infection has been satisfactorily treated [5,21,29,31,32]. The interval between removal of a prosthesis and resolution of infection may be as much as 40 weeks [24,26,29].

We used an Ilizarov ring fixator to achieve arthrodesis when other techniques would be difficult to apply, thereby avoiding above-knee amputation. Ilizarov fixation has several technical advantages: 1) continuous axial compression, which may stimulate bone healing and subsequent resolution of osteomyelitis [33,34]; 2) excellent stability; 3) application in the presence of active infection; 4) versatility, which means that it can be used when the bone ends are fractured, with massive bone loss, severe osteoporosis, or when a hip prosthesis is present; and 5) no requirement for bone grafting. We present our initial experience with this technique.

Patients and Methods

Between 1991 and 1998 we performed arthrodesis of the knee with the Ilizarov fixator after failed TKA due to deep sepsis in 15 patients (14 women, 1 man) whose mean age was 74 years (55 to 90). Details of the patients are given in Table 1. The indication for TKA was osteoarthritis in 11 patients, rheumatoid arthritis in three and avascular necrosis in one. Twelve prostheses had been implanted in other hospitals and three in ours. The prosthesis was hinged in five patients and a resurfacing design in ten. Seven patients presented with an infected TKA and eight with a failed arthrodesis after removal of an infected implant. The mean interval between the initial operation and removal of the prosthesis was 42 months (1 to 130). Since the amount of available cancellous bone is important for the fusion, we classified the loss of bone at the time of operation as follows: 1) Mild. Full bony contact is possible with congruous and almost continuous cancellous surfaces. 2) Moderate. There is incomplete bony contact with loss of cancellous bone after the removal of the tibial or femoral components, or a long-standing pseudarthrosis following a failed arthrodesis. 3) Severe. There is minimal bony contact and two cone shaped shells of cortical bone without cancellous contact. Bone loss was mild in two patients (Fig. 1a), moderate in eight (Fig. 1b) and severe in five (Fig. 1c). The knees were approached through the previous, usually anteromedial parapatellar, incision. If present, the prosthesis and all cement were removed. Fibrous tissue and bone samples were taken for microbiological studies. Minimal resection of the tibial and femoral bone ends was performed. If possible, the patella was used as autograft, but no other bone graft was used. The Ilizarov fixator consisted of two rings around each segment of bone. Two crossed transfixation wires, under 130 kg tension, were placed on each ring. The bone ends were approximated as accurately as possible. Threaded bars were placed between the rings to initiate axial compression on the bone ends (Fig. 2), and intermittent compression was applied by 1 mm at three-week intervals. Appropriate antibiotics were given for at least six weeks after surgery. Two patients with negative cultures were treated with gentamicin and a second-generation cephalosporin. When radiological signs of consolidation appeared, and the knee was considered to be clinically fused, the frame was removed, and a cast was applied for at least six weeks. The patients were allowed to bear weight on the limb during the whole period of treatment if able. Complications were classified according to Paley [35] and were events, which required surgical intervention or caused residual deformity.

Results

The results of bacterial cultures are shown in Table 2. In all patients the infection healed without recurrence. Arthrodesis was achieved in all but one patient (Table 3). The mean duration of application of the Ilizarov frame was 28 weeks (16 to 54), the mean time of immobilisation in a cast 23 weeks (7 to 65) and the mean total length of treatment was 51 weeks (26 to 106). The mean follow-up was for 52 months (14 to 91). Seven patients had no complications, but all had a mean discrepancy in limb-length, due to bone loss, of 4 cm (2 to 6). This was unavoidable and we did not deem it a complication. All had pin-track infections, which were successfully treated with flucloxacillin given orally. There were 15 complications in eight patients. Three were not related to the arthrodesis: these were an urinarytract infection in two patients and pneumonia in one. In eight patients there were 12 complications related to the treatment according to the classification system of Paley [35] an incidence of 80%. Pin-track osteomyelitis necessitated intravenous antibiotics in three patients and the infected pins were removed. In one patient a fracture of the femur and tibia occurred during removal of the prosthesis, but the Ilizarov frame was nevertheless applied. In another patient, a fracture of the femur occurred at the tip of the stem of the knee prosthesis, two weeks after application of the frame. The frame was then extended to incorporate the proximal part of the femur. Half-pins used for fixation at the proximal end of the femur, became loose 21 weeks later and the frame was reapplied. There was malunion of the fracture and the patient developed a decubitus ulcer of the heel. In two patients the fixation became loose, and was successfully reapplied. In one patient who had an earlier attempted arthrodesis with an allograft in the referring hospital, nonunion occurred after removal of the Ilizarov frame. This was treated by a knee orthosis.

All but one of the complications were treated without residual deformity. During follow-up, two patients died in institutions for the elderly and their cause of death was not investigated.

Discussion

Deep infection is a very serious complication of TKA, which usually requires removal of the implant and attempted arthrodesis. Orthopaedic surgeons will be confronted increasingly with this problem as the number of TKA's performed increases, especially in younger patients. Intramedullary nailing has been the most reliable method of achieving arthrodesis with a rate of union of 94% [24]. Two studies with small groups of patients [26,29] reported union in 100% (Table 4). This technique has two significant disadvantages. First, arthrodesis can be effected only after the infection has been successfully treated [5,21,29,31,32]. The interval between the removal of the prosthesis and the eradication of the infection may be up to 40 weeks [24,26,29]. Secondly, autologous bone grafting should be performed at the same time. Our experience using the Ilizarov technique in 15 patients gave a rate of union of the knee arthrodesis of 93%. This is of particular significance since eight patients (53%) had undergone earlier attempts at arthrodesis in other hospitals; most had long-standing osteomyelitis, and were elderly (Table 4).

The rate of complications related to treatment was 80%. Other techniques referred to in Table 4 show rates of 25% to 75%. We did not, of course, expect this rate to be lower than that previously reported using different techniques. Although the rate of complications was high, the rate of union was also high.

Many complications in our study were related to poor quality and quantity of available bone. In three patients, loosening of fixation pins was due to poor bone quality. In one patient, the femur and tibia fractured during the removal of the prosthesis, because of very poor bone stock. In the patient with nonunion abundant allografting had been performed in an attempt to achieve arthrodesis elsewhere. We decided not to remove the allograft when we applied the fixator. No graft was used in any other patient.

The mean total duration of treatment with this technique was 51 weeks. With intramedullary nailing shorter treatment times have been reported [24,26]. When the arthrodesis is performed under adverse clinical conditions as when the infection is hard to control, the treatment time may be more than one year [29]. An Ilizarov arthrodesis has the advantage that it can be performed in the presence of active infection. The infection subsides with continuous axial compression and treatment with antibiotics, and the arthrodesis proceeds to union [33,34]. In our study there were no recurrences of infection.

A major disadvantage of the Ilizarov external ring fixator is its bulkiness which causes considerable discomfort. Our experience of knee arthrodesis using the Ilizarov method in patients in whom arthrodesis after removal of infected knee arthroplasty could be difficult to achieve with other techniques has been satisfactory.

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Table 1. Details of the 15 patients who had arthrodesis of the knee

Case	Age (year)	Gender	Diagnosis	Type of TKA	Where TKA was removed	Interval between TKA implantation and removal (months)	Bone loss
1	67	Female	Osteoarthritis	Resurfacing	Elsewhere	8	Moderate
2	78	Female	Osteoarthritis	Resurfacing	Elsewhere	14	Moderate
3	90	Female	Osteoarthritis	Resurfacing	Our hospital	13	Mild
4	73	Male	Rheumatoid arthritis	Resurfacing	Our hospital	54	Moderate
5	86	Female	Osteoarthritis	Hinged	Our hospital	77	Severe
6	76	Female	Rheumatoid arthritis	Hinged	Our hospital	130	Severe
7	55	Female	Avascular necrosis	Resurfacing	Our hospital	45	Moderate
8	87	Female	Osteoarthritis	Hinged	Elsewhere	71	Severe
9	78	Female	Rheumatoid arthritis	Hinged	Our hospital	99	Severe
10	60	Female	Osteoarthritis	Resurfacing	Elsewhere	1	Mild
11	63	Female	Osteoarthritis	Resurfacing	Elsewhere	4	Moderate
12	76	Female	Osteoarthritis	Resurfacing	Our hospital	19	Moderate
13	69	Female	Osteoarthritis	Resurfacing	Elsewhere	2	Moderate
14	82	Female	Osteoarthritis	Hinged	Elsewhere	69	Severe
15	81	Female	Osteoarthritis	Resurfacing	Elsewhere	100	Moderate

Table 2. Bacterial cultures from infected knee arthroplasty

	Number of patients
Staphylococcus aureus	6
Staphylococcus epidermidis	1
Haemolytic streptococcus group G	1
Moxarella species	1
Pseudomonas aeruginosa	1
Klebsiella pneumoniae	1
Enterococcus, peptostreptococcus and an anaerobic rod	1
Staphylococcus aureus, Escherichia coli and *Pseudomonas aeruginosa*	1
Negative cultures	2

Table 3. Details of the arthrodesis performed in each of 15 patients

Case	Follow-up (months)	Frame application time (weeks)	Cast immobilisation time (weeks)	Total treatment time (weeks)	Limb-length discrepancy (cm)	Complications (Paley [35])
1	91	20	14	34	3	None
2	82	16	10	26	2	None
3	63	22	29	51	6	None
4	76	17	52	69	2	Pneumonia
5	8	29	8	37	5	*
6	73	18	16	34	4	None
7	72	16	14	30	3	Osteitis
8	71	37	65	106	5	#
9	63	22	56	78	5	None
10	49	34	35	69	4	Osteitis
11	46	54	15	69	3	Frame instability
12	31	33	7	40	4	None
13	24	32	7	39	4	None
14	23	52	22	74	6	Frame instability
15	14	40	8	48	3	Nonunion

* Fracture of femur and tibia at removal, urinary-tract infection

osteitis, fracture of the femur ‘at the tip’, frame instability, angulation of femur after fracture, heel decubitus and UTI

Table 4. Results of knee arthrodesis after infected knee arthroplasty in the literature

Author	Number of infected TKAs*	Technique	Healing rate (%)	Mean treatment time (months)	Age (year (range))	Complications (%)
Lai et al [24]	31	IM nailing	94	6	68 (61 to 78)	24
Puranen et al [26]	8	IM nailing	100	4	66 (46 to 84)	13
Vlasak et al [29]	7	IM nailing	100	18	55 (34 to 72)	-
Wilde & Stearns [30]	12	IM nailing	67	-	66 (49 to 77)	75
Brodersen et al [20]	40	#	84	-	62 (35 to 83)	-
Rand et al [17]	25	EF¶	60	-	65 (34 to 84)	68
Rothacker & Cabanela [27]	29	EF¶	86	-	65 (34 to 84)	28

* number of patients with infected TKAs resulting in arthrodesis being performed

Miscellaneous external fixation

¶ External Fixator

Fig. 1a

Fig. 1b

Fig. 1c

Radiographs showing knees with a) mild, b) moderate and c) severe bone loss.

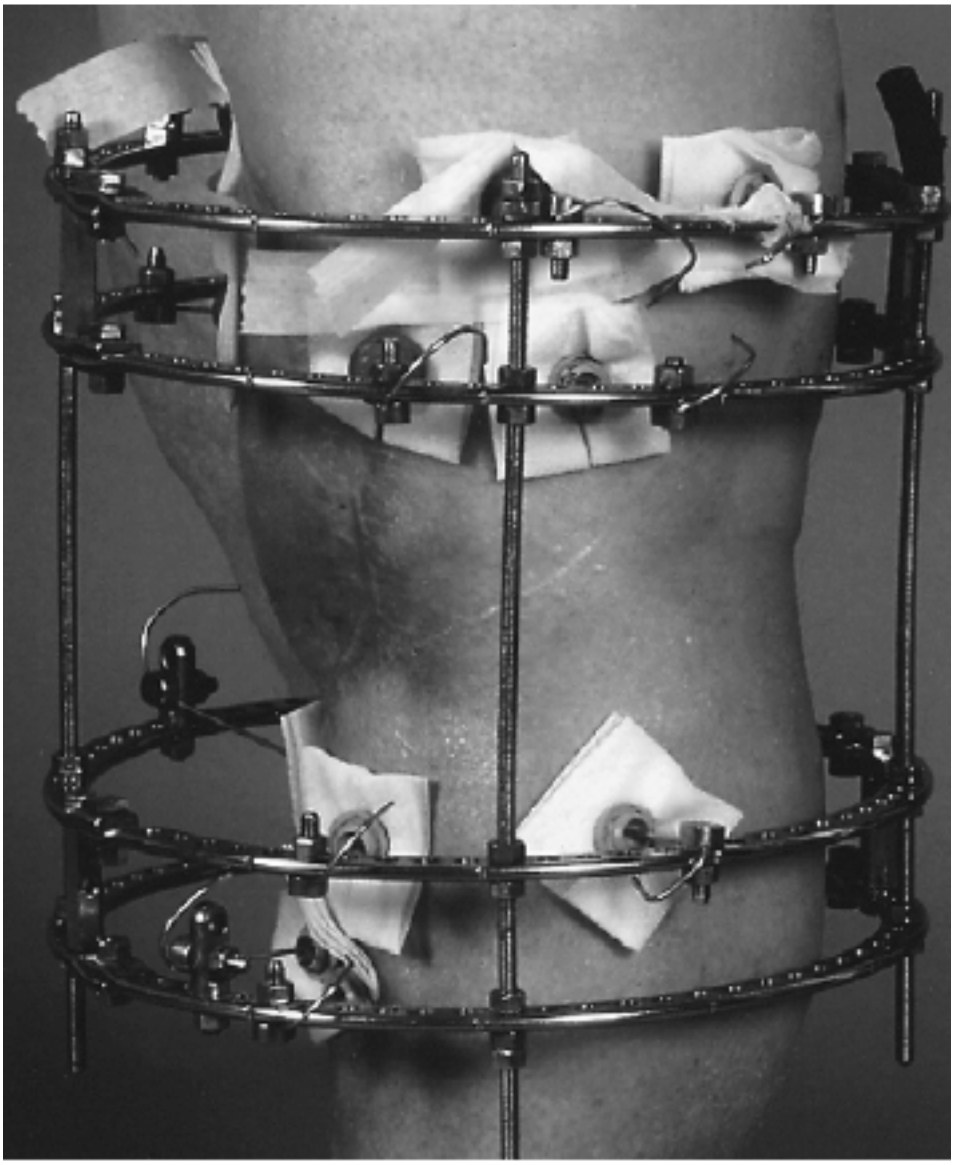

Fig. 2

Photograph showing an Ilizarov frame for knee arthrodesis.

Chapter 8

General discussion

Limb reconstruction results improved considerably, and new applications appeared, since the introduction of the Ilizarov technique in the Western world in the early 1980's.
In 1990 the Ilizarov technique was introduced in the Netherlands at the University Medical Centre Utrecht (UMCU). From clinical observations, several questions were raised about the effects, results and complications of this type of treatment. This is the topic of this thesis.

A total of six retrospective and experimental studies were set up to answer the questions as defined in the introduction:
I. What are the results of limb lengthening and reconstruction in growing individuals?
II. What is the effect of limb lengthening on the remaining spontaneous growth of the limb, and is any factor recognizable that might influence the growth rate during and after limb lengthening in growing individuals?
III. Can growth stimulation be exerted by joint distraction in tibial lengthening?
IV. Can growth plate technetium scintigraphy be used as a predictor for the future growth rate?
V. Which are the results of limb lengthening and reconstruction in adult post-traumatic deformities?
VI. Is knee arthrodesis with the Ilizarov method a good option for the salvage of failed knee arthrodesis after infected knee arthroplasty?

1. What are the results of limb lengthening and reconstruction in growing individuals?

A great variety of factors, many of them patient related, influence the desired results in limb lengthening. Obviously, the degree of length discrepancy and the desired amount of lengthening poses technical problems and limitations, as well as does the anatomical site, for instance tibia, femur, or both. Also, the aetiology or pathogenesis of the deformity, like acquired or congenital, plays an important role in the eventual outcome. Age of the patient (adult or child), concomitant factors that may compromise the end result, like contracted, dysplastic or unstable adjacent joints, neurological disorders, and many other factors must be taken into account when assessing treatment strategies and prognosis [1-3]. How

these factors influence the outcome has not been investigated so far. When all concomitant factors are adequately anticipated, as may be expected from experienced surgeons, many complications can be prevented. An important example is dislocation of the congenitally unstable knee during distraction. When the joint is bridged with the fixator, this complication does not occur.
In chapter 2, in a polytomous universal mode (PLUM) logistic regression approach, factors that may influence the complication rate in children were analyzed. The analysis shows that only relative or proportional (percentage) length discrepancy, not the absolute length discrepancy (in centimetres) was a significant predictor of the complication rate. The analysis also allowed constructing a simple model for the probability of complications as a relation to relative length discrepancy. This model shows a significant, but weak relation between relative length discrepancy and the probability of complications during lengthening. It means that, in our population, the general risk of 1 or more obstacles and complications is about 50% [1]. We hope that our model will enable comparison between clinics and patient populations; therefore validation outside our practice is necessary to demonstrate general applicability.
A limitation of this study is that we were not able to differentiate the patient related complications from the surgeon related complications. It may be assumed that in an experienced and well functioning limb lengthening unit, patient factors are predominant, because the learning curve has been overcome [2].

2. What is the effect of limb lengthening on the remaining spontaneous growth of the limb, and is any factor recognizable that might influence the growth rate during and after limb lengthening in growing individuals?

In literature, conflicting information is available on how limb growth is affected by lengthening procedures; both retardation and stimulation were reported. Several mechanisms are proposed for these effects, the most probable is an excessive loading or relieve unloading of the growth plate during lengthening, respectively [4-11]. Trauma to the femur in children causes overgrowth of the affected limb that may result in a permanent length discrepancy of up to 2 centimetres. This indicates that trauma to a limb, especially the upper leg, induces a biological growth stimulus [12]. How this stimulus works remains largely unknown, but it is suggested that growth factors deriving from the bone repair are dissipating to the growth plate [13-17], increased blood flow playing a role as well [18]. This effect is temporary but may cause up to 2 centimetre extra growth of the leg. It

seems logical that the fracture needs to be proximal to the knee growth plates, where about 70% of the total limb growth occurs. This is the reason that we focused on the knee during lengthening procedures. Since growth retardation and stimulation are reported, it can quite safely be argued that compression, as is seen in joint cartilage [19-21], or unloading of the knee growth plates [6] is the explanation for the conflicting observations. In the Utrecht procedures, several children had limb lengthening with bridging of the knee to stabilize the knee during lengthening. After the lengthening, at the start of the consolidation phase of the distraction callus, the knee fixation was removed. This type of treatment resulted in a significant extra growth stimulation of the treated leg. On top of the inherent growth of the limb, a significant extra growth, in one case even overgrowth as compared to the healthy side, was recorded, and this was described in chapter 3. If the knee would be permanently fixed in an Ilizarov frame during the many months of callus distraction, gradual compression on the included growth plates should be the resultant effect of the inherent growth of the same growth plates. Fixation of the growth plates as in guided growth results in growth retardation. So, in knee bridging, distraction of the joint was envisaged and performed. In knee distraction, an external fixator is applied to the upper and lower leg.
Therefore, two interventions, namely knee joint distraction and an external fixator on the upper leg, either each by itself, or together, can be responsible for growth stimulation.

3. Can growth stimulation be exerted by joint distraction during tibial lengthening?

This question was addressed in an experimental study.
As indicated in the previous section, conflicting information in literature indicates that growth retardation and stimulation are both observed after limb lengthening in children [4-11]. During analysis of the data in the clinical study as presented in chapter 3, the question was raised how the growth plates react to the trauma or biological stimulus of bone/soft tissue/limb lengthening in paediatric limb reconstruction. The results from the clinical study indicated that joint distraction and/or the application of a joint bridging external fixator may cause growth stimulation in a limb that is otherwise growing slower than the healthy side. An experimental study in rabbits was set up to investigate the hypothesis that unloading of the proximal tibial growth plate during tibial lengthening may stimulate the growth rate of the lengthened bone, in this case the tibia. The possible stimulating effect of an extensive external fixation frame was addressed by the application of a sham femoral fixator during lengthening of the tibia.

The effect of the application of a femoral fixator is, in itself, a significant stimulation on the growth rate when the tibia is lengthened. It is uncertain how joint distraction affects the growth rate. This factor showed a measurable, but non-significant growth stimulus in this study.
The small study groups may subjectively be the weakness of this study. However, the number of measurements and the unanimous results in every test animal make the outcome significant and relevant.

4. Can growth plate technetium scintigraphy be used as a predictor for the future growth rate?

Simultaneous with the experiment as described in chapter 4, we wanted to know whether growth speed could be correlated to or deduced from scintigraphic activity of the involved growth plates [22-24]. This was done in a parallel experimental study as described in chapter 5. The study was designed to investigate whether it is possible to anticipate the effect of limb lengthening and joint distraction on the growth rate. Although we could show that growth stimulation is possible, a doctor always wants to know to what extent his intervention affects the outcome, in this case the length discrepancy. Other studies have suggested that, in an experimental situation, a relation exists between growth rate and scintigraphic activity of the growth plate [22-24]. In an unpublished clinical case, we could confirm that. Unfortunately, we could not show any relation between growth rate and scintigraphic activity of the proximal tibial growth plate in our experiment. We have no explanation for this outcome. Possible factors may be unloading of the lengthened limb, and subsequent less calcification of the bone, less bone mass in the lengthened limb, systemic errors in the setup of the experiment, measurement errors caused by the tiny size of the bone, et cetera. There are too many possible explanations to investigate in the available material.

5. Which are the results of limb lengthening and reconstruction in adult post-traumatic deformities?

The study to answer this question, as described in chapter 6, has the same setup and research question as in chapter 2. The difference is the patient group. In chapter 6, adult lower limb reconstruction, indicated by post-traumatic deformities, was investigated. The patient group was analysed with the same methods. As in children, the proportionate length discrepancy was the only significant factor affecting the complication rate. The rate was comparable with results from literature when broken down to

each complication type as well as in general [3, 25]. There is a much stronger relation between the proportionate length discrepancy and the complication rate as compared to children. In 10 % discrepancy, the risk for 2 or more complications is about 32%, and in 20% discrepancy about 50%. Since our model is new, application in other clinics will have to show the validity of the model.
Limb reconstruction seems to be effective in (post) traumatic deformities. However, the question that every healthcare worker, public healthcare manager, insurer, and foremost the patient asks is whether this demanding treatment is worth the effort and suffering of the patient, and the cost. This has been investigated in reconstruction of severely traumatized limbs like in Gustilo type 3B-C fractures, where standard osteosynthesis procedures may not be applied. Limbs can be saved from amputation with the Ilizarov or a similar technique with at least an equal functional result, and less healthcare burden than amputation [26-32]. Nevertheless, every patient with this type of injury will keep functional limitations.

6. Is knee arthrodesis with the Ilizarov method a good option for the salvage of failed knee arthrodesis after infected knee arthroplasty than other reported techniques?

As a tertiary referral centre for arthroplasty infections, a new application for the Ilizarov treatment in the UMCU was developed in knee arthrodesis as salvage for resection arthroplasty in untreatable total joint replacement infection. A clinical retrospective study was done to investigate the results of this type of treatment compared to other techniques reported in literature. In chapter 7 the results of this technique are described.

The standard solution for infected arthroplasty is removal of the implant, debridement down to healthy tissue and antibiotic treatment guided by per-operatively obtained tissue cultures, imaging, blood tests as ESR and CRP, and the clinical picture. With 1 or 2-stage revisions, the majority of infections can successfully be treated, success rates ranging from 77-91% have been reported in the literature [33-36].
Sometimes, infection cannot be eradicated with standard regimens, and reimplantation of an arthroplasty therefore is not possible. Resection arthroplasty, like the Girdlestone situation in the hip, is not an effective option for the knee, and arthrodesis is the best option under these circumstances. The only alternative, above the knee amputation, is obviously a much less desirable outcome [37]. Recently, a report was presented showing again that revision after TKA infection is most likely to fail in 20%. In those unfortunate patients, knee arthrodesis seems to be the

most effective treatment for functional reasons as well as to cure the infection [38].
Several treatment regimens to obtain an arthrodesis of the knee are available, but eradication of infection is a prerequisite for most. Especially internal fixation, in a post-infected environment often with poor soft tissue conditions, has many drawbacks and risks. Application of ORIF techniques is only possible in eradicated infection. At the same time, mechanical stability is often helpful in obtaining ultimate resolution of infection. This is a conflicting situation. Therefore, external fixation has received much attention [36, 39-51].
External fixation with a monolateral fixator is a possible option, but bone fixation is frequently a problem in this often vulnerable, fragmented (Type 3) and still infected bone [52]. The Ilizarov method has many theoretical and practical advantages in this type of a situation. Multiple pins from many angles can be used to enhance fixation, compression can very well be applied and the excellent stability is beneficial for the cure of any remaining infection.
All our patients had a solidly united knee arthrodesis in a good position, with elimination of the infection and a weight bearing leg in the end. No amputation was needed, even in very old and fragile patients.
These results compare favourably with all other methods reported in the literature [36]. The drawback of this treatment is a, very uncomfortable time of 'wearing' the Ilizarov frame, which takes a mean period of about one year.

General remarks, epicrisis.
The Ilizarov method of limb reconstruction is a very powerful tool for bone, soft tissue, and limb repair and regeneration. More recently, these principles have been adapted for new devices as the Taylor spatial frame, or the TL-Hex system, using a hexapod system, combining the principles as described by Ilizarov with modern day computer technology, but this is not the topic of this dissertation. Despite the rather uncomfortable, time consuming and intensive treatment, it is more reliable and versatile in the severest of trauma and deformity cases compared to other treatment options, because it allows treatment of a limb with soft tissue sparing, and can be combined by gradual correction of the defect or deformity. Variants of the Ilizarov frame are now available in the healthcare market. Especially, the Hexapod variant is interesting, because it is easier to perform 3 dimensional corrections. Hexapods allow re-corrections much easier than the Ilizarov system, if the initial correction does not work out as anticipated. However, the versatility of the Ilizarov system is unrivalled. It is like the old Cold War between two systems: the western, easy-to-use, but sometimes

not so reliable, computer directed system, against a very reliable, but labour-intensive, mechanical system.

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Chapter 9

Summary and conclusions

After the introduction of the Ilizarov method in the West, a number of clinical problems could be addressed, which formerly were part of the unresolved medical problems. Although limb lengthening was practiced before, the results were rather unpredictable and the treatment was very frequently accompanied with a lot of serious complications. With the Ilizarov method limb lengthening was more under control. The method consists of several principles:

1. Gradual distraction or distraction osteogenesis and histiogenesis after a latency period.
2. Versatility: angulation, torsion and translation deformities could be corrected at the same time as the lengthening. Bone transport was a total new concept that was developed in Ilizarov's clinic
3. Respect for the biological structures: mainly bone marrow and periosteum. Minimal trauma to the bone and soft tissues that compose the environment for histiogenesis.
4. Nonlinear stiffness in axial direction by tensioned transfixation wires in a circular frame.
5. Physiological use of the lengthened limb.
6. Continuous compression in infected nonunion cures the infection and the nonunion.

Ilizarov and followers explored new applications besides simple limb lengthening. The main specialties that took advantage of the Ilizarov technique were paediatric and trauma orthopaedics. Niche applications were arthrodesis, joint distraction, and reconstruction of metabolic, tumorous or skeletal dysplasia deformities. Now certain deformations could be treated, and the necessity of lifelong orthoses could be taken away in many cases. There is a cost benefit also.

Side effects come with new tools. It is very demanding for the patient in terms of long duration of pain, limited mobility for many months up to several years caused by the treatment and the bulky circular external fixator, dependency on the social and family circle.
The treatment still comes with many complications. Since the possibilities are increasing, more daring treatments are initiated, and these inevitably come with more complications.

This thesis aims at clarifying several of the new aspects of the Ilizarov treatment.
The research questions were as follows.

I. What are the results of limb lengthening and reconstruction in growing individuals?

II. What is the effect of limb lengthening on the remaining spontaneous growth of the limb, and is any factor recognizable that might influence the growth rate during and after limb lengthening in growing individuals?

III. Can growth stimulation be exerted by application of a fixator to the femur with or without joint distraction during tibial lengthening?

IV. Can growth plate technetium scintigraphy be used as a predictor for the future growth rate?

V. Which are the results of limb lengthening and reconstruction in adult post-traumatic deformities?

VI. Is knee arthrodesis with the Ilizarov method a good option for the salvage of failed knee arthrodesis after infected knee arthroplasty?

In chapter 1, the consequences of the introduction of the Ilizarov method in the western countries are discussed. The new concepts of histiogenesis by gradual distraction, limb deformity correction and minimal trauma surgery are introduced. New applications have been found. The negative aspects of this method are surveyed also. A new application for knee arthrodesis after chronically infected total knee arthroplasty, developed in Utrecht (by PMvR) is described. An experiment is designed for the investigation of the growth rate of lengthened legs in children. The outline of the thesis is defined. Six research questions are formulated; distilled from collected patient data since the introduction of limb lengthening and reconstruction with the Ilizarov method in Utrecht.

In chapter 2, an analysis of the complications rate of limb reconstruction in a cohort of 37 consecutive growing children was done. Several patient and deformity factors were investigated by logistic regression in a polytomous ordinal regression model. The only independent statistical factor influencing the complication rate was the initial relative limb length discrepancy. A simple graph was constructed, allowing comparison of the results with other reconstruction units.

In chapter 3, the lower limb reconstruction of a cohort of 30 growing children, followed up for at least 2 years, and still growing, has been analyzed. The analysis is focused on the reaction of the paediatric limb to the trauma of lengthening. 15 patients showed increased growth rates in the operated limb compared to the pre-operative growth rate. This was statistically related to large frames including the femur and tibia with joint distraction.

In chapter 4 the results of an experiment are described. The documented increased growth rate after paediatric lengthening was further investigated in an animal experiment. The concept is that the application of a femur external fixator and joint distraction could have a stimulative effect on the growth plate of the proximal tibia during tibial lengthening. The results are very constant; the application of a femoral Ilizarov frame during tibial lengthening stimulates tibial growth significantly after the lengthening. Joint distraction has a minor additional effect to the application of a femoral frame in all animals; the difference however was not significant.

Chapter 5 describes the scintigraphic reaction in the growth plates during and after the experiment as described in chapter 4. It was thought that the scintigraphic activity of the growth plates would reflect the biological activity during and after lengthening procedures. Unfortunately, no relation between growth rate and scintigraphic activity of the growth plates could be shown. Several possibly explanations are discussed, but no definitive cause for the findings could be found.

In chapter 6, the lower limb reconstruction of 52 patients with post-traumatic deformities was analyzed. The treatment failed in only 3 patients; in 1 patient biological reasons could be traced; in 2 patients a non-coping behaviour resulted in failure. This stresses the necessity of pre-operative psychological screening. As described in chapter 2, the analysis of the patient data by logistic regression in a polytomous ordinal regression model showed that the relative limb length discrepancy (bone loss in percentage) was the sole factor influencing the complication rate. Again a graph was constructed, showing the relation between complication risk and relative limb length discrepancy/bone loss. This profile shows that the 50% risk threshold for 1 or more complications is 8% limb length discrepancy, for 2 or more complications it is 16%, for 3 or more complications 31%.

In chapter 7, arthrodesis of the knee after failed arthrodesis for infected knee arthroplasty was analyzed. This is the first publication in literature with this solution for this particular problem. Again the Ilizarov method is a welcome adjuvant. The concepts of Ilizarov's method (see the summary of chapter 1) was well illustrated with the union of 14 out of 15 patients and total resolution of the infection in all 15 patients. The success rate of union and infection control has not been reported before.

In chapter 8, the findings of all investigations are discussed and put in a context for daily practice. For paediatric applications, it is shown that lengthening with bulky Ilizarov fixators including a joint (with joint distraction) stimulates growth. The effect is not temporary and remains throughout the remaining growth period. This effect should be anticipated when starting lengthening procedures in children. Complications in limb lengthening are only related the relative amount of length discrepancy, no other factor is of influence. The method of analysis resulted in the construction of a simple graph, allowing comparison of results with other limb construction units, independent from the patient mix.
Finally, knee arthrodesis with the ilizarov method showed to be a new development with the most reliable outcome with respect to eradication of the infection and union rate of the arthrodesis compared the any other method that has been used before.

Chapter 10

Samenvatting en conclusies

Toen de Ilizarov methode in de Westerse wereld werd geïntroduceerd kon een aantal klinische problemen worden opgelost, waarvoor tot die tijd geen goede behandeling voor handen was. Beenverlenging werd op beperkte schaal al uitgevoerd, maar de resultaten waren onvoorspelbaar en er traden zeer vaak ernstige complicaties op. Met de Ilizarov methode werd verlenging een beter controleerbare behandeling. Deze methode wordt gekenmerkt door een aantal basis principes:

1. Verlenging tussen botfragmenten met geleidelijke distractie ofwel distractie osteogenese en histiogenese na een latentie periode.
2. Flexibiliteit: angulatie, torsie en translatie van botsegmenten kan tegelijkertijd worden uitgevoerd. Bot transport was een nieuwe toepassing, ontwikkeld in Ilizarov's kliniek.
3. Respect voor de biologische structuren: beenmerg en periost moeten gespaard worden. Beperk het operatieve letsel aan bot en weke delen die de omgeving van de histiogenese bepalen.
4. Non-lineaire stijfheid in de axiale richting dankzij de transfixatie draden van de circulaire fixateur.
5. Zo normaal mogelijk gebruik van het verlengde been
6. Continue compressie op de geinfecteerde boteinden laten infectie en pseudarthrose genezen.

Ilizarov en zijn volgers en medewerkers hebben allerlei nieuwe toepassingen voor histiogenese geëxploreerd. Met name kinderorthopaedie en traumatologie hebben hiervan geprofiteerd. Nieuwe toepassingen zijn arthrodese, gewrichtsdistractie, reconstructie van allerlei skeletafwijkingen door dysplasie , of metabole en tumoreuze aandoeningen. Daardoor konden allerlei deformiteiten worden hersteld en de noodzaak tot levenslang gebruik van ortheses worden weggenomen. Daar zit ook een kosten beperking aan vast.

Met nieuwe methodes komen nieuwe bijwerkingen. Deze behandelmethode veroorzaakt veel pijn, beperkte mobiliteit gedurende maanden tot jaren door onder andere de forse maten van de fixateur externe, verder grote afhankelijkheid van andere mensen.
Er treden veel complicaties bij op. Door de verruimde mogelijkheden worden uitdagender oplossingen geprobeerd, die ook meer problemen en complicaties veroorzaken.

Enkele nieuwe aspecten van de Ilizarov methode worden in dit proefschrift besproken. De onderzoekvragen zijn daarbij als volgt:

I. Wat zijn de resultaten van beenverlenging en reconstructie bij groeiende mensen?
II. Wat is het effect van been verlenging op de te verwachten groei van een ledemaat en is er een factor te identificeren die deze verdere groei beïnvloedt?
III. Kan men groei stimuleren door een fixateur externe te plaatsen op het femur met of zonder kniegewricht distractie bij tibia verlenging?
IV. Kan men met technetium scintigrafie van groeischijven toekomstige groei voorspellen?
V. Wat zijn de resultaten en complicaties van post-traumatische secundaire ledemaat reconstructie bij volwassenen.
VI. Is knie arhtrodese met de Ilizarov techniek een goede 'salvage' behandeling bij gefaalde knie arthrodese voor geinfecteerde knie arthroplastiek?

In hoofdstuk 1 wordt de effecten besproken van de introductie van de Ilizarov methode in het Westen. Het nieuwe concept van histiogenese door geleidelijke distractie, ledemaat reconstructie en chirurgie met zo klein mogelijk letsel aan het te verlengen weefsel worden uitgelicht. De nieuwe toepassingen worden aangegeven. De keerzijdes van dit type behandeling wordt eveneens besproken. Een nieuwe toepassing is knie arthrodese als laatste oplossing voor geïnfecteerde knieprothese, dit werd in Utrecht ontwikkeld door Peter van Roermund. Een studie opzet voor onderzoek naar het effect van beenverlenging op de verdere groei van kinderbotten wordt voorgesteld. De opzet van dit proefschrift wordt besproken en zes onderzoeksvragen geformuleerd aan de hand van de patienten gegevens uit Utrecht.

Hoofdstuk 2 behandelt de analyse van gevolgen en complicaties van Ilizarov ledemaat reconstructie bij een aaneensluitende groep van 37 kinderen. Patient en deformiteit factoren worden onderzocht in een model van logistische regressie in een polytome ordinale regressie. The enige onafhankelijke statistische factor die het aantal complicaties blijkt te beïnvloeden is de relatieve of het percentage beenlengteverschil. Een overzichtelijke schematische figuur waarin deze gegevens zijn verwerkt geeft het effect aan van het beenlengteverschil op het aantal complicaties en maakt vergelijking tussen de resultaten van ledemaat reconstructie afdelingen mogelijk.

In hoofdstuk 3 wordt de analyse beschreven van wat de effecten van been verlenging zijn op de overblijvende groei in een groep van 30 kinderen. Bij 15 kinderen zagen we een vorm van groeistimulatie in het behandelde been. Er was een statistische relatie te leggen met het gebruik van Ilizarov fixateurs die op boven- en onderbeen worden geplaatst en waarbij dan knie distractie werd uitgevoerd.

In hoofdstuk 4 wordt een dier experiment beschreven waar bij de groeistimulatie zoals beschreven in hoofdstuk 3 verder wordt geanalyseerd. Het gebruik van een femur fixateur en knie distractie bij tibia verlenging kan de groeistimulans verklaren. Het effect is telkens reproduceerbaar en het blijkt significant bij het gebruik van een femur fixateur in dit experiment, waarbij knie distractie een trendmatige, niet significante groeistimulatief effect heeft. Enkele verklarende oorzaken worden besproken.

In hoofdstuk 5 wordt bekeken of de toekomstige groei(stimulans) als beschreven in hoofdstuk 4 kan worden voorspeld met technetium scintigrafie van de proximale tibia groeischijf. Er blijkt geen enkele relatie te zijn met het groeipatroon. Potentiële oorzaken voor deze waarneming worden besproken.

In hoofdstuk 6 worden de ledemaat reconstructies van 52 patiënten met een post-traumatische deformiteit geanalyseerd op identieke wijze met logistische regressie als de patiënten groep uit hoofdstuk 2. De data tonen opnieuw aan dat de mate van het relatieve/percentage beenlengteverschil of botlengte verlies de enige factor is die gerelateerd is aan het risico op complicaties. Opnieuw werd een figuur gemaakt waarin schematisch dit effect wordt aangegeven. Het toont bijvoorbeeld dat er 50% kans is op 1 complicatie bij een beenlengteverschil van 8%, op 2 complicaties bij 16% en 3 bij 31%.

Arthrodese voor aanhoudende infectie na het verwijderen van een knie prothese is het onderwerp van hoofdstuk 7. De uitvoering hiervan met de Ilizarov methode is een totaal nieuwe toepassing in de literatuur. De Ilizarov methode blijkt een zeer effectieve toepassing te zijn met 14 succesvolle behandelingen bij 15 patienten wat betreft fusie en genezing van de infectie.

In hoofdstuk 8 worden alle bevindingen bediscussieerd en krijgen zij een plaats in de dagelijkse praktijk. Voor pediatrische toepassing blijkt een grote fixateur met de knie erin én met knie distractie groeistimulatie te induceren. Dit lijkt een blijvend effect te zijn en heeft dus consequenties bij kinderbeenverlengingen. Complicaties bij kinderbeenverlengingen zijn slechts zwak gerelateerd aan het percentage beenlengteverschil, terwijl dit bij volwassenen een veel sterker effect blijkt te hebben. Constructie van een grafiek met daarin de relatie weergegeven tussen percentage beenlengteverschil en aantallen complicaties aan de hand van patiënten dat maakt vergelijking mogelijk tussen ledemaat reconstructie behandelcentra onafhankelijk van de patiënten mix. Tot slot, knie arthrodese met de Ilizarov techniek is een nieuwe toepassing met de meest betrouwbare resultaten met betrekking tot fusie en eradicatie van de infectie tot nog toe beschreven.

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Curriculum vitae

Hubert Oostenbroek was born on 8 December 1958 in Amsterdam. He attended kindergarten (Het Begin) and primary school (De Pijlstaart) in Vinkeveen. He attended secondary school at Vossius Gymnasium in Amsterdam. Between 1977 and 1987, he studied medicine in Amsterdam at the Vrije Universiteit, interrupted by a period of over 2 years. Between 1987 and 1993, he was a resident not in training in BovenIJ Ziekenhuis Amsterdam (emergency doctor), Medisch Centrum Alkmaar (general surgery and orthopaedics), and University Medical Centre Utrecht (orthopaedics).

In 1993, he started his formal training in general surgery in the Clara Ziekenhuis Rotterdam (dr. T.I. Yo), and continued for his formal orthopaedics training in UMCU (prof. dr. A.J. Verbout), MCA (dr. W.J. Willems) and Onze Lieve Vrouwe Ziekenhuis (prof. dr. J.W. van der Eijken) until 1999. In 1999 he followed a fellowship in paediatric orthopaedics in Wilhelmina Kinder Ziekenhuis (dr. J.H. Pruijs).

In 2000 and 2001 he was registrar orthopaedics in the Antonius Ziekenhuis in Nieuwegein, in 2002 he moved on to Leiden University Medical Centre as a consultant, and reached his assumed professional destination in 2007 in Haga Ziekenhuis/Juliana Kinder Ziekenhuis in The Hague as a consultant paediatric orthopaedic surgeon.

Hubert is married to Jorinde Bisschop; they have 1 son, Maurits (1994). The Oostenbroek family lives in Wassenaar since 1993.