



The role of Taylor Spatial Frame for the treatment of acquired and congenital tibial deformities in children

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This study evaluates the use of the Taylor Spatial Frame (TSF) for the correction of acquired and congenital tibial deformities in children. The purpose is to underline problems, obstacles and complications that can be observed during treatment to reveal the learning curve and potential risk factors and to propose solutions to avoid difficulties during its use 86 tibia deformities were corrected in 66 children during a period of 7 years and were classified according to anatomical and dominant type of deformity. Follow up was 54.2 months. Gradual correction was performed according to the individualized time schedule. We faced 42 difficulties : 29 problems, 10 obstacles and 3 complications, distributed across all years. Significant correlation was found between patient's age and number of difficulties. The incidence of the difficulties was equally spread over the different etiologies, but it was statistically significant across the years.

Proximal tibia and complex multi-plane deformities seem to be related to an increased incidence of postoperative difficulties. TSF can yield accurate results, is easy to handle and provides an excellent concomitant 3-direction correction.

Keywords : Taylor spatial frame ; external fixator ; tibia deformities ; children.

INTRODUCTION

Acquired and congenital long bone deformities are common clinical entities in pediatrics, and the

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External fixation is a valuable treatment in the management of limb deformities allowing gradual correction of complex long bones axial deviations with minimal soft tissue trauma, minimizing risk of neurovascular injury and allowing greater amounts of correction. Various types of external fixators

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have been used, including monolateral fixators, circular frames and hybrid systems. Correction of multiplanar deformities, however, still remains the major challenge for all these systems (*12,19,21,22,24*).

The Taylor spatial frame (TSF), introduced by Charles Taylor in 1994, is a circular frame with a hexapod strut configuration, that permits a simultaneous six axes correction of deformities. By adjusting only the strut's length, one ring can be repositioned in respect to the other, in all space dimensions. A web-based software program is used to calculate a daily prescription schedule for strut adjustment. In cases of residual axial malalignement or planned staged correction of a deformity, a second program can easily be created.

TSF has the capability of six axes correction. Prior to TSF clinical implementation, corrections were performed after application of external fixation in a sequential way, often necessitating device alterations, taking place at patients' bedside, and prolonging treatment time as well as patient's anxiety. Studies reported that the TSF compares favorably with standard external ring fixators, especially with regard to accuracy and patient comfort (*5,8,9,14*).

This study aims to reveal potential risk factors in using the TSF for the correction of tibia deformities in children, to determine the learning curve and propose possible solutions to avoid difficulties in using this specific fixation system.

MATERIALS AND METHODS

A series of 66 children (89 tibiae), treated with the TSF from January 2005 to December 2011, was retro-

spectively analyzed; 36 were males (54,55%) and 30 females (45,45%) with a mean age of 11.15 years (range 3-16 years).

Inclusion criteria were : (1) patient age less than 16 y, (2) presence of a multi planar deformity of the tibia, (3) treatment of the deformity by TSF and (3) frame removal before April 2012.

Exclusion criteria were defined as: (1) follow-up < 1 y, (2) TSF for segmental bone transport, (3) other types of external or internal fixation used before or during treatment, (4) absence of appropriate radiographs of the lower extremity before and after surgical procedure or at the time of follow-up visits.

Preoperative diagnoses are presented in Table I. We classified our cases according to the anatomical site (Table II) and dominant type of deformity (Table III), to search for potential differences regarding incidence of observed problems, obstacles and complications between different groups.

Preoperative clinical and radiographic evaluation and TSF surgical planning were performed. Preoperative radiographic planning included the assessment of (i) the angular deformity in the sagittal and frontal plane with antero-posterior and lateral views of the leg, (ii) the rotational deformity from CT scans or clinical evaluation, and (iii) leg length discrepancy from a scanogram of the lower extremities.

Data were inserted in the software program SPATIALFRAME VERSION 3.1 TM of Smith & Nephew, which directed, postoperatively, the sequence of strut lengthening and shortening, and drove the spatial motion of the two circular frames accomplishing the preoperatively designed correction of the deformity. The individualized time schedule included a limit on the distraction allowed daily, determined by the surgeon. Time for TSF removal was determined by bone healing shown on X-rays.

| Diagnosis | Nº Limb | Percentage | Problems | Obstacles | Complications | Time of Treatment |
|--|---------|------------|----------|-----------|---------------|-------------------|
| Blount's disease | 24 | 27,9 | 8 | 3 | - | 3,4m 11,1d |
| Axes deviation in neuromuscular conditions | 21 | 24,6 | 3 | - | 1 | 3,5m 14,3d |
| Hemimelia | 12 | 13,7 | 7 | 5 | - | 6,1m 19,9d |
| Post traumatic tibia deformities | 11 | 12,8 | 3 | - | - | 3,2m 17,5d |
| Tibial Leg discrepancy | 6 | 6,9 | 6 | 2 | - | 5,5m 18d |
| Achondroplasia | 6 | 6,9 | 1 | - | 1 | 7,6m 11d |
| Unilateral valgus Knee | 3 | 3,6 | - | - | 1 | 3,6m 12,6d |
| Tibial pseudarthrosis | 3 | 3,6 | 1 | - | - | 3.3m 24,3d |
| Total | 86 | 100% | 29 | 10 | 3 | |

Table I. - Preoperative diagnosis

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|------------------------------|------------------|--------------------|----------|-----------|---------------|
| Anatomical site of deformity | N° Limb | % | Problems | Obstacles | Complications |
| Proximal tibia | 43 | 50 | 22 | 9 | 2 |
| Tibial mid shaft | 21 | 24,42 | 4 | 1 | 0 |
| Distal tibia | 22 | 25,58 | 3 | 0 | 1 |
| Total | 86 | 100% | 29 | 10 | 3 |

Table II. – Anatomical site of deformity

| Table III | Dominant type | e of the deformity |
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|----------------------------|---------|-------|----------|-----------|---------------|
| Dominant type of deformity | N° Limb | % | Problems | Obstacles | Complications |
| Varus | 1 | 1,16 | 1 | 0 | 0 |
| Valgus | 12 | 13,95 | 4 | 2 | 0 |
| Anterior-procurvatum | 3 | 3,48 | 1 | 0 | 0 |
| Posterior-recurvatum | 2 | 2,35 | 0 | 0 | 0 |
| Rotational | 12 | 13,95 | 1 | 0 | 0 |
| Length discrepancy | 0 | 0 | 0 | 0 | 0 |
| Combined | 56 | 65,11 | 24 | 8 | 3 |
| Total | 86 | 100% | 29 | 10 | 3 |

Surgery was performed by a single senior surgeon and under general anesthesia (in supine position). To reduce duration of surgery, the frame was prebuilt by the surgeon preoperatively, mimicking roughly the deformity and using a sterile table in the same operating room. To fix the rings to the bone, both wires and half-pins were utilized. The multiple drill hole technique was applied for the tibial osteotomy reducing the potential thermal bone necrosis by the oscillating saw ; for the osteotomy of the fibula, Linston bone scissors were used. Distraction started within 7-9 days after surgery. Gradual correction followed the individualized time schedule, provided by the computer software, and parents were instructed by a responsible health care professional.

In case of a tibial lengthening larger than 30 mm, the frame was also fixed to the foot, following Ilizarov's recommendations, to avoid development of equino-varus deformity. The foot ring was removed 40-60 days after the end of correction once the soft tissues were stretched sufficiently, thus allowing range of motion exercises of the ankle joint.

Paley's criteria were used to evaluate difficulties in using TSF, including postoperative assessment of all problems, obstacles and complications related to TSF, from the time of surgery till 1y after the frame's removal (19).

Problems were defined as any potential difficulties arising during the treatment period and fully resolved by

the end of the process, by non-operative means. Pin track infection, docking drift, wound breakdown, software changes and delayed consolidation, belonged to this category.

Obstacles were defined as any potential difficulties arising during the period of treatment and fully resolved by the end of the process by operative means. Non-union, joint contracture, fracture through regenerated bone, recurrences of deformation and fracture at the docking site belonged to this category.

Complications were defined as any local or systemic complication (intraoperative/postoperative), or difficulty found during the stretching or stabilization, that remained unresolved until the end of the treatment period, and any early or late difficulty, observed after treatment. Persistent knee contraction, amputation due to non-union/poor regenerate bone or persistent infection, reflex sympathetic dystrophy and neurological disturbances belonged to this category.

Statistical analysis was performed using SAS statistical package v 9.2 (SAS Institute Inc., Cary, North Carolina). To compare the incidence of various problems, obstacles and complications, we assessed the data for normality. The Gaussian distribution was tested with the Kolmogorov-Smirnov test, and the mean values of the subgroups were compared with Student's t-test. Nonparametric variables were compared using the MannWhitney test. One-way analysis of variance (ANOVA) was used to assess the effect of multiple factors, and level of significance was set at p - < 0.05.

RESULTS

86 tibial deformities were corrected in 66 children within a period of 7 years. 26 cases were operated on the right side only, 20 on the left and 20 were bilateral. The mean follow-up time was 54.2 months (range 16-84 months).

According to Paley's criteria, we found 42 difficulties, 29 problems, 10 obstacles and 3 complications (Table IV).

The overall difficulty from the use of TSF was not significantly different over the years, but tended to be higher in 2005 and 2007. However, the incidence of problems was statistically significantly different over the years (p = 0.047).

A significant correlation was observed between the age of the patient at the time of surgery and the number of difficulties (r = 0.0325, p < 0.001). The incidence of problems, obstacles and complications did not differ between the different etiologies (p = 0.143) and the mean time of treatment for each diagnosis (p = 0.141) (Table I). However, there was a statistically significant difference when comparing the anatomical site of deformity (p < 0.00001)with the proximal tibia being associated with an increased incidence of postoperative difficulties according to Paley's criteria (Table II). Moreover, cases with multi-plane deformities were associated with a statistically significant increase of incidence of postoperative problems and complications, when compared to single-plane deformities (p = 0.00001)(Table III).

DISCUSSION

The aim of our study was to evaluate the TSF for the treatment of acquired and congenital tibial deformities in children. Problems, obstacles and complications associated with the procedure were evaluated.

We observed that the anatomical site of deformity at the proximal tibia, and complex multi-plane deformities, were related to a statistically significant



Fig. 1. – Pin track infection

increase in incidence of postoperative problems and complications.

The most common problem observed in all years was pin tract infection, observed in 12 of the 516 pin and wires used (2,32%) in 13,95% of tibias treated, which is consistent with the current literature. To classify and treat pin tract infection Gordon's grading system was used (12). We observed 7 Grade 1 (pain, erythema, or tenderness around the pin site), 3 grade 2 (characteristics of grade 1 infections, but with serous drainage) and 2 grade 3 (characteristics of grade 1 infections, but with purulent drainage). Few reports exist on the superficial infection progressing to a deep infection (17) or osteomyelitis. In our series no cases of radiographic osteolytic changes to the pin sites (grade 4) or ring sequestrum/osteomyelitis (grade 5) were observed. Pin-site infections were resolved by oral antibiotics (amoxicillin 20 mg/kg twice a day for 5 days) (11,15) except one, which required intravenous antibiotics and one half pin removal (Fig. 1).

Software changes were mostly observed in 2007 (50%), also the year with the highest number of cases needing multi planar corrections; in the subsequent years, need for software changes were less, probably due to the learning curve.

Delayed consolidation maybe observed during treatment with TSF. Dynamic loading is recommended and can be obtained by replacing TSF struts with Ilizarov rods, or to back out the struts, to obtain some compression, or take out some wires and/or

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|--|------|-------|----------|----------------|------------|---------------|------|--|--------|-------|------|------|------|-------|-------|
| Problems | 2005 | % | 2006 | % | 2007 | % | 2008 | % | 2009 | % | 2010 | % | 2011 | % | Total |
| Pin track infection | 3 | 25 | 1 | 8,33 | 2 | 16,66 | 1 | 8,33 | 2 | 16,66 | 1 | 8,33 | 2 | 16,66 | 12 |
| Software changes | 5 | 14,29 | ю | 21,42 | 7 | 50 | 5 | 14,29 | 0 | 0 | 0 | 0 | 0 | 0 | 14 |
| Delayed consolidation | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 33,33 | 0 | 0 | 0 | 0 | 2 | 66,66 | ю |
| Total | 9 | 20,69 | 4 | 13,8 | 6 | 31,03 | 4 | 13,8 | 5 | 6,9 | 1 | 3,5 | 4 | 13,8 | 29 |
| Obstacles | | | | | | | | | | | | | | | |
| Non union | - | 33.33 | 0 | 0 | 1 | 33.33 | 0 | 0 | 0 | 0 | 0 | 0 | - | 33.33 | ю |
| Fracture deformation of the regenerated bone | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 33.33 | 0 | 0 | 0 | 0 | 2 | 66.67 | 3 |
| Recurrence of deformation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 66,67 | 0 | 0 | 1 | 33,33 | 3 |
| Fracture at docking site | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - | 100 | 1 |
| Total | 1 | 10 | 0 | 0 | 1 | 10 | 10 | 18,18 | 5 | 20 | - | 10 | 3 | 30 | 10 |
| Complications | | | | | | | | | | | | | | | |
| Joint contracture | 0 | 0 | 1 | 33,33 | 0 | 0 | 1 | 33,33 | 0 | 0 | 0 | 0 | 1 | 33,33 | 3 |
| Total | 0 | 0 | 1 | 33,33 | 0 | 0 | 1 | 33,33 | 0 | 0 | 0 | 0 | 1 | 33,33 | 3 |
| | | | | | | | | | | | | | | | |

Table IV. - Distribution of problems, obstacles and complications by year

pins. The less wires/pins left in the bone, the more dynamic load is applied. Also, removal of one of the struts allowing patient's full weight bearing on the frame permits more dynamic load. Since this will break the hexagonal construct and make the whole frame unstable, removing one or more struts of the TSF is subject to fractures, if the bone is not healed enough (6,11). In our series 3 cases of delayed consolidation were observed. In 2 cases extension of the external fixation time and dynamic loading was decided, when the rings were parallel by changing the struts with Ilizarov rods. In the third case casting was performed for 40 days and full bearing. No fractures related to early frame removal or dynamic loading were observed.

A specific obstacle of TSF's use, also observed in our study, is the fracture of the regenerated bone, Eidelman et al (8) reviewed their experience on the use of TSF in both tibia and femur and suggested that removing the frame, relying on radiographic evidence, is inadequate for determining the extent of bone healing and advocated dynamic loading of the frame to prevent fractures. Another study also recommended dynamic loading of the frame prior to removal (20) while different authors use to place their patients in a Sarmiento brace, after frame removal to protect the regenerated bone (7). Therefore, it is beneficial to protect the bone after frame removal, to prevent injury to the newly formed bone. In our series 3 cases were observed and TSF was replaced by a uniplane fixator during 40-60 days.

Nonunion was observed in 3 patients and they subsequently underwent bone grafting and application of growth factors, extending the external fixation time by about 50 days (16). Nonunion may occur during frame treatment, although it should be avoidable when TSF is used.

Recurrence of deformity was observed in 3 children, affected by Blount's disease, because the family did not follow exactly the instructions and the software program. In one of them, TSF was newly applied after one year, while for the remaining 2 cases plating was performed 4 months after TSF's removal.

Fracture at the docking site was also observed in only one patient and a uniplane fixator replaced TSF.

It is well known that there exists a potential risk for posterior subluxation of the knee when an external fixation treatment is selected, including the TSF. Although it is mostly associated with correction of a severe deformity, during major lengthening, simultaneous femoral and tibial lengthening's, and in inherently unstable knee joints, Jones and Moseley (13) reported a posterior knee subluxation even in a small distraction of only 2.5%. However, no posterior subluxation of the knee joint, in preoperatively stable knees, was observed in our study.

Knee stiffness was present in 3 patients and an intensive physical therapy program was started immediately with a final regain of 80% of knee ROM in 2 of them while one needed a Judet's quadrice-plasty, 2 years after surgery.

Different authors in their studies reported complications after using TSF. Sluga *et al* (21) reported pin tract infections, temporary knee stiffness, and pin breakage. Fadel and Hosny (9) reported, pin tract infections in all patients (12 required antibiotics), adjustment under anesthesia in 6, frame loosening in 3, early consolidation in 3, fracture of the regenerate in 2, after premature removal of the fixator, and deep vein thrombosis in 1. These authors additionally reported that patients had problems to follow the instructions of the TSF protocol.

As limitations of our study should be mentioned that patients were reviewed retrospectively and all data were retrieved from charts, giving a number of factors that might have biased the results, a common finding in most studies ; also, outcome measures are based on the subjective assignment of end points and changing definitions of complications (15).

Generally, deformity correction is demanding and has a steep learning curve (4). External fixation is a valuable treatment option used for the management of tibia deformities and allows for gradual correction of complex situations, with minimal soft tissue trauma. TSF, with its hexapod strut configuration, permits a simultaneous six axes correction of deformities, by only adjusting the length of struts, which is dictated by a web-based software program. Residual correction with the TSF requires no return to the operating room and, therefore, less morbidity for the patient and less work for the surgeon (12). Sluga *et al* recommended the use of the TSF due to its ease of use and low complication rate, after only 5 patients treated with this device (21). Other authors reported a steep learning curve, using the TSF, and preferred using the Ilizarov device in their environment (9). However, the choice of external fixator is generally determined by the experience and preference of the surgeon, the complexity of the problem, and the number of sites that need to be corrected (1).

In our study, we found differences in the incidence of complications, obstacles and problems in the application of the TSF throughout the period of its use. This was related to relevant differences in the complexities of deformities that were corrected, but also, to the improvement of the surgical skills of the surgeon.

TSF was well accepted by children making them more secure and confident during mobilization and weight bearing, even if it is cumbersome. The goal of treatment was achieved in all patients and TSF seems to be a valid method to treat bone deformities in children, especially when it involves deformities with more than one plane and requiring simultaneous correction in sagittal frontal and axial planes. However, due to the remarkably high cost, it has not yet been established as our routine device.

REFERENCES

- 1. Aronson J. Limb-lengthening, skeletal reconstruction, and bone transport with the Ilizarov method. *J Bone Joint Surg Am* 1997; 79: 1243-1258.
- Birch JG, Samchukov ML. Use of the Ilizarov method to correct lower limb deformities in children and adolescents. *J Am Acad Orthop Surg* 2004 ; 12 (3) : 144-54. Review.
- **3. Blondel B, Launay F, Glard Y, Jacopin S, Jouve JL, Bollini G.** Hexapodal external fixation in the management of children tibial fractures. *J Pediatr Orthop B* 2010; 19 (6): 487-491.
- **4. Dahl MT, Gulli B, Berg T.** Complications of limb lengthening. A learning curve. *Clin Orthop Relat Res* 1994 ; 301 : 10-18.
- Docquier PL, Rodriguez D, Mousny M. Three-dimensional correction of complex leg deformities using a software assisted external fixator. *Acta Orthop Belg* 2008; 74 (6): 816-822.
- **6. Eidelman M, Zaidman M, Katzman A.** Treatment of posttraumatic deformities in children and adolescents using the Taylor Spatial Frame. *Orthopedics* 2010; 33 (4): 253-256.
- 7. Eidelman M, Katzman A. Treatment of complex tibial fractures in children with the Taylor Spatial Frame. *Orthopedics* 2008; 31 (10): 992.

- Eidelman M, Bialik V, Katzman A. Correction of deformities in children using the Taylor spatial frame. *J Pediatr Orthop* B 2006; 15 (6): 387-395.
- **9. Fadel M, Hosny G.** The Taylor spatial frame for deformity correction in the lower limbs. *Int Orthop* 2005 ; 29 : 125-129.
- Feldman DS, Madan SS, Ruchelsman DE, Sala DA, Lehman WB. Accuracy of correction of tibia vara : acute versus gradual correction. *J Pediatr Orthop* 2006 ; 26 (6) : 794-798.
- 11. Feldman DS, Madan SS, Koval KJ, van Bosse HJ, Bazzi J, Lehman WB. Correction of tibia vara with six-axis deformity analysis and the Taylor Spatial Frame. *J Pediatr Orthop* 2003; 23 (3): 387-391.
- **12. Gordon JE, Kelly-Hahn J, Carpenter CJ, Schoenecker PL.** Pin site care during external fixation in children : results of a nihilistic approach. *J Pediatra Orthop* 2000 ; 20 (2) : 163-165.
- **13.** Jones DC, Moseley CF. Subluxation of the knee as a complication of femoral lengthening by the Wagner technique. *J Bone Joint Surg Br* 1985; 67: 33-35.
- 14. Marangoz S, Feldman DS, Sala DA, Hyman JE, Vitale MG. Femoral deformity correction in children and young adults using Taylor spatial frame. *Clin Orthop Relat Res* 2008 ; 466 (12) : 3018-3024.
- Moroni A, Caja VL, Stea S, Visentin M. Hydroxyapatite coating external fixation pins versus uncoated. *Bioceramics* 1993 ; (6) : 239-44.
- 16. Naqui SZ, Thiryayi W, Foster A, Tselentakis G, Evans M, Day JB. Correction of simple and complex pediatric deformities using the Taylor-Spatial Frame. *J Pediatr Orthop* 2008; 28 (6): 640-647.
- Noonan KJ, Leyes M, Forriol F, Can^adell J. Distraction osteogenesis of the lower extremity with use of monolateral external fixation. A study of two hundred and sixty-one femora and tibiae. *J Bone Joint Surg Am* 1998; 80: 793-806.
- **18. Paley D.** Problems, obstacles, and complications of limb lengthening by the Ilizarov technique. *Clin Orthop Relat Res* 1990; 250: 81-104
- Price CT, Scott DS, Greenberg DA. Dynamic axial external fixation in the surgical treatment of tibia vara. *J Pediatr Orthop* 1995 Mar-Apr; 15 (2): 236-43.
- **20. Rozbruch SR, Pugsley JS, Fragomen AT, Ilizarov S.** Repair of tibial nonunions and bone defects with the Taylor Spatial Frame. *J Orthop Trauma* 2008 ; 22 : 88-95.
- **21. Sluga M, Pfeiffer M, Kotz R** *et al.* Lower limb deformities in children : two-stage correction using the Taylor Spatial Frame. *J Pediatr Orthop B* 2003 ; 12 : 123-128.
- 22. Stanitski DF, Srivastava P, Stanitski CL. Correction of proximal tibial deformities in adolescents with the T-Garches external fixator. *J Pediatr Orthop* 1998; 18: 512-517.
- **23. Tetsworth KD, Paley D.** Accuracy of correction of complex lower-extremity deformities by the Ilizarov method. *Clin Orthop Relat Res* 1994 ; 301 : 102-110.