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Original Article

Mechanobiology in the management of mobile atrophic and oligotrophic tibial nonunions

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ABSTRACT

Background: Recent research indicates that atrophic nonunions are biologically active and may heal in the optimal biomechanical environment.

Methods: Thirty-three patients with mobile atrophic and oligotrophic tibial nonunions were treated with circular external fixation and functional rehabilitation. Seven patients required autogenous bone graft procedures.

Results: Bony union was achieved after the initial surgery in 31/33 (93.9%) tibias. Two persistent nonunions were successfully treated with repeat circular external fixation without bone graft. This resulted in final bony union in 33/33 (100%) patients.

Conclusion: Mechanobiological stimulation of tibial nonunions can produce union even if the biological activity appears to be low.

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1. Introduction

The clinical entity of tibial nonunion incorporates a variety of conditions that range from mobile to stiff, hypertrophic to atrophic, with deformity or without, and even large segmental bone defects, with or without limb length discrepancy.^{1–3} The proposed management of these subdivisions is almost as numerous as the variation in nonunions themselves, and even within groups, the management can be affected by host factors, condition of the surrounding soft tissues, and the nonunion morphology itself.^{2,4}

The treatment of tibia nonunions is mostly based on small series of cases that frequently include a variety of nonunion subtypes and even infected cases.^{2,5,6} Fixation methods vary from internal fixation, including conventional compression plating, locked plating, and reamed intramedullary nailing, to external fixation, with either monolateral fixators, circular fixators, and hybrid fixators.^{2,5,7,8} Some authors have proposed cast immobilization and isolated fibula osteotomy.⁹ Adjuvants to surgical management include the use of autogenous bone graft, autologous bone-marrow aspirate, bone morphogenetic proteins (BMPs), low-intensity ultrasound, and hyperbaric oxygen.^{10–15} This lack of uniformity in the available literature

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has rendered the establishment of an evidence-based, reproducible protocol for the management of tibial nonunions difficult, if not impossible.

In this retrospective review, we focus on the management of mobile atrophic and oligotrophic tibial nonunions. We report our results of a uniform series of tibial nonunions treated by circular external fixation. In addition, we aim to show that the correct biomechanical environment can promote bone healing without the need for routine bone graft and expand on the concept of mechanobiology in the management of tibial nonunions.

2. Methods

From January 2010 to January 2014, 36 patients with mobile atrophic and oligotrophic tibial nonunions were treated at our tertiary level limb reconstruction unit. Three patients were excluded because they did not complete the proposed treatment. These included a 33-year-old male and a 44-year-old female, and both died of systemic complications of chronic disease. Both these patients were HIV positive and developed nonunion following open fractures. The third patient presented to our unit three years after sustaining an open fracture. He was a chronic smoker and his previous treatment included three different external fixators, cast immobilization, internal fixation, and surgery for metalware removal. This patient was unwilling to continue reconstruction after 12 weeks in a circular external fixator and requested amputation.

Nonunions were defined as at least six months time elapsed since the fracture and union deemed unlikely without further intervention. Nonunions were classified according to radiographic appearance on preoperative radiographs. Atrophic nonunions demonstrated no callus formation or periosteal reaction while minimal callus formation designated oligotrophic nonunions. Nonunions were further classified as mobile if more than 7° motion was possible at the nonunion site. Motion was assessed preoperatively and then confirmed intraoperatively following fibula osteotomy. There were 22 atrophic and 11 oligotrophic nonunions as determined by preoperative radiographs.

Open fractures were the initial injury in 20 patients. Nine injuries were Gustilo-Anderson IIIB, nine Gustilo-Anderson IIIA, and two Gustilo-Anderson II open fractures.^{16,17} Four patients had tibia fractures following gunshots and three of these patients had emergency fasciotomies at the time of injury. Nine patients had closed fractures; five were initially treated by closed manipulation and cast immobilization and the other four were treated by intramedullary, interlocked nails (Fig. 1). Duration of nonunion ranged from six to 192 months since the initial injury, with a mean of 25 months.

A standard physical, laboratory, and radiographic evaluation was performed on all patients as per protocol. Any modifiable risk factors that were identified were optimized. These included cessation of smoking, optimal glycemic control in diabetics, and the commencement of highly active antiretroviral therapy for HIV positive patients with low CD₄ counts, prior to surgical intervention. All patients with

Fig. 1 – Antero-posterior and medio-lateral radiograph of tibial nonunion 10 months after intramedullary nail.

infected nonunions were excluded. Screening consisted of a detailed history to exclude any previous wound drainage, sinus formation, or treatment for infection of the nonunion site. This was supplemented with clinical and laboratory evaluation that consisted of complete blood count, erythrocyte sedimentation rate, and C-reactive protein level.

Partial fibula resection prior to circular external fixator application was performed in all cases. Resection was performed under tourniquet control and at the level of the fibular deformity if present. Direct surgical approach between the peroneal and soleus muscles was made. The fibula was exposed by subperiosteal dissection and a small oscillating saw was used to resect approximately 10 mm of fibula to prevent early fibular consolidation. Fascia and skin were closed in layers over a drain. The tourniquet was deflated for the remainder of the operation.

External fixation started with a custom prebuilt frame for each patient. Standard frame construct consisted of a four-ring frame with two rings making up a ring block for each bone segment. Frame application proceeded in a stepwise approach starting with proximal and distal reference wires, followed by gradual nonunion reduction as fixation is added toward the two middle rings of the frame.¹⁸ Frames were applied in a hybrid method, using a combination of tensioned fine wires and maximum two hydroxyapatite (HA) coated half pins. Once mechanical alignment and stable fixation were achieved, the nonunion site was compressed manually by adjusting the distance between the proximal and distal ring blocks (Fig. 2).

The nonunion site was not routinely exposed or debrided and bone graft was only used for specific indications. These

Fig. 2 – Standardized antero-posterior and medio-lateral radiograph after fine wire circular external fixator application.

included nonunions where the bone contact area after compression was less than 50% of the normal bone diameter. Bone graft procedures consisted of iliac crest autogenous cancellous on-lay grafting.

Functional rehabilitation was encouraged with the assistance of a physiotherapist. This entailed early joint mobilization and weight bearing followed by normalization of gait pattern and functional use. Pin track care was according to our standard protocol and included twice daily cleaning with an alcoholic solution of chlorhexidine.¹⁹

Outpatient follow-up was scheduled at two weekly intervals until a robust rehabilitation routine was established. Thereafter, the follow-up was increased to four weekly intervals. Fixator removal was considered once tricortical consolidation was seen. At this juncture, a staged 'trial of union' protocol was initiated. Firstly, the external fixator was completely dynamized by loosening all connections between the ring blocks and stressing the union site manually. If this did not cause any pain or deformity, the patient was instructed to bear weight. If the patient was able to walk without pain, he was allowed to return home with a fully dynamized frame and encouraged to mobilize full weight bearing for a period of two weeks. Repeat radiographs at follow-up were compared with radiographs from prior two weeks. If no deformity occurred during this trial period, union was confirmed and the external fixator was removed. All patients were followed up clinically and radiologically for a minimum of six months after frame removal. Any changes in angulation from previous visits were identified as a failure of treatment.

3. Results

The medical records and serial radiographs of all 33 patients were reviewed. The study population consisted of 29 men and four women with a mean age of 34 years, ranging from 18 to 73 years. Follow-up ranged from six to 43 months, with an average of 13 months, after external fixator removal (Table 1).

Risk factors for nonunion development were identified in 29 patients (87.8%). These included open fractures ($n = 19$), compartment syndrome ($n = 3$), smoking ($n = 14$), and diabetes ($n = 5$). The remaining four patients all had closed fractures with no apparent risk factor for nonunion formation. Four patients were HIV positive (12%). These patients had a mean CD4 count of 369 cells/mm³ (range 200–603) and were all on antiretroviral therapy.

The Ilizarov fixator (Smith & Nephew, Memphis, TN) was used in nine cases and the TrueLok fixator (Orthofix, Verona, Italy) in 24 cases. There was no statistically significant difference in union rates or complications between patients treated with the Ilizarov or TrueLok fixators. The average length of time in external fixator was 22 weeks, ranging from eight to 53 weeks.

Bony union was achieved after the initial treatment in 31 out of 33 (93.9%) tibias (Fig. 3). Two patients had failure of treatment after initial treatment. Both patients had atrophic nonunions. The first was a 34-year-old male, who sustained a closed tibia fracture that was initially treated with a locked intramedullary nail. This patient healed after repeat treatment in a fine wire circular fixator. Failure of the initial nonunion treatment was due to the erroneous early removal of the circular external fixator. The second patient sustained an open tibia fracture that was initially treated with a monolateral external fixator. After 23 weeks in the initial circular external fixator, his nonunion became hypertrophic and was successfully treated with conversion to a hexapod circular external fixator and closed distraction. Failure of the initial circular fixator treatment was probably due to unstable fixation. This resulted in final bony union in all 33 tibias (100%).

Pin track infection was the most common complication experienced and occurred in 5/33 cases (15%). The majority of these infections was minor according to the Checketts and

Table 1 – Details of results.

Patients	33
Males	29
Females	4
Mean age (years)	34 (18–73)
Type of nonunion	
Atrophic	22
Oligotrophic	11
Average time to nonunion surgery (months)	25 (6–192)
Fixator	
Ilizarov	9
TrueLok	24
Average healing time (weeks)	22 (8–53)
Iliac autograft	7

Fig. 3 – Antero-posterior and medio-lateral radiograph of united tibia 12 months after external fixation removal.

Otterburn classification and responded to oral antibiotics and local pin track care.²⁰ One patient developed a grade VI infection of a HA pin site. This pin site was debrided with the Versajet Hydrosurgery System (Smith & Nephew, Memphis, TN) and subsequently healed uneventfully.

4. Discussion

It is generally accepted that hypertrophic nonunions need mechanical stability to heal while atrophic nonunions need mechanical stability and biological stimulation.²¹ Biological stimulation in this setting often refers to bone grafting of the nonunion site due to the perceived biological inactivity of these nonunions.^{3,21,22} Biological stimulation can, however, also be provided by creating the ideal mechanical environment, the concept of mechanobiology.^{8,23–25}

The biological inactivity of atrophic bone ends has been questioned by authors in recent literature.^{24,26–29} Brownlow et al.²⁶ and Reed et al.²⁷ showed that the vascularity of atrophic nonunions is comparable to that seen in fresh fractures and hypertrophic nonunions. Ismail et al.²⁹ showed that mesenchymal stem cells were present at the site of atrophic nonunions at similar number and viability than those isolated from the iliac crest. Sun et al.²⁸ postulated that these mesenchymal stem cells were temporarily quiescent and could be reactivated under certain conditions. Kloen et al.²⁴ documented the presence of BMP-signaling components in long-standing atrophic nonunions. These studies have shown that atrophic nonunions are biologically active on a vascular,

cellular, and biochemical level. This biology could be stimulated and enhanced under the correct biological environment.^{24,30} We have shown in our results that 26 out of 33 (78%) atrophic and oligotrophic nonunions healed without the need for autogenous bone graft.

The use of bone graft, however, cannot be completely abandoned. In our series, we used autograft in seven cases (21%). These involved nonunions where the bone contact area after reduction was <50% of the original bone diameter. Although these nonunions may still have united, the refracture risk after external fixator removal prompted the use of autograft to increase the diameter of the union site.

Creating the ideal mechanical environment for bone healing can be accomplished with the use of fine wire circular external fixation.^{31,32} These fixators have the ability to provide stability against translation and rotation in the coronal and sagittal plane while still allowing a degree of axial micro motion to stimulate bone formation.^{33,34} The circular fixator also affords the required stability to allow early rehabilitation without the need for any period of protected weight bearing.³⁵

The choice and configuration of the external fixator is vitally important in the management of mobile nonunions. Unlike stiff hypertrophic nonunions that have intrinsic stability that can be manipulated, atrophic nonunions have to rely solely on the stability provided by the external fixator and compression at the nonunion site. As such, the classic Ilizarov frame design with ring blocks for each bone segment and spanning the entire length of the tibia provides the most stability and was used in all our cases.

Mechanical stimulation is the foundation of all nonunion management and can be effective in creating union even in the presence of atrophic bone ends.²⁴ Ilizarov stated that functional load determines the structure, shape, and volume of any limb. This is due to a local increase in blood flow during functional use that aids in tissue growth.⁸ Mechanical stimulation also directly influences bone biology on a cellular level by stimulating the proliferation and differentiation of osteoblasts.^{8,25} Mechanical stimulation has further benefits in terms of union site remodeling as a result of piezoelectrical charges that are generated in response to mechanical stresses. Osteoblasts on the compressive side are stimulated as a result of electronegative charges while osteoclasts are activated by electropositive charges on the tension side.^{25,36} Mechanical force application patterns, loading magnitude, and frequency also affect bone healing on a biochemical level.²⁵ The rates of synthesis and degradation of extracellular matrix components are affected by force application patterns. Loading magnitude affects cell size through increased amounts of intermediate filaments and glycogen particles while changes in loading frequency can alter mRNA synthesis of anabolic and catabolic genes.²⁵ Aggrecan gene expression is increased in response to mechanical stimulation and leads to an increased proteoglycan scaffold for type II collagen.⁸

Fibula osteotomy has been shown to have low complication rates and to be effective in treating delayed union or nonunion of the tibia.^{9,37} It is an important step in the management of tibial nonunions for two reasons. Firstly, a mobile fibula will allow correction on any tibial deformity, if present. Secondly, partial fibula resection will increase compressive forces across the nonunited tibia to stimulate bone healing.^{37,38} Dujardin

et al.³⁷ consider the fibula osteotomy as an essential part of the treatment for tibial nonunions to allow sufficient compression when used in combination with the Ilizarov frame.

There are several limitations to this study, including its retrospective design, single-center site, and lack of a control group. The series is also confined to tibial nonunions and may not necessarily be extrapolated to nonunions of other anatomical regions.

5. Conclusion

Mechanobiological stimulation, through the use of fine wire circular external fixation and functional rehabilitation, can predictably produce union of mobile atrophic and oligotrophic tibial nonunions. This treatment is effective without the need for routine bone graft even if the biological potential appears to be low.

Conflict of interest

The authors have none to declare.

Ethical statement

The study was authorized by the local ethics committee (BE 086/14) and performed in accordance with the Ethical standards of the 1964 Declaration of Helsinki as revised in 2000.

Authors' contributions

All three authors made contributions toward the conception and design of the research, acquisition of data, and drafting of the manuscript. The final manuscript was read and approved by all the authors.

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