ORIGINAL ARTICLE

Effectiveness of teriparatide combined with the Ilizarov technique in septic tibial non-union

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ABSTRACT

Aim The septic non-union is a common compliance in bone healing due to bone infection. Bone resection, associated with Ilizarov osteo-distraction technique, is commonly used in these cases. The aim of this study was to analyse clinical and radiological results of teriparatide in combination with the Ilizarov technique and to compare this treatment with the standard treatment.

Methods Forty adult patients underwent surgery because of type C of the Association for the Study and Application of Methods of Ilizarov (ASAMI) classification non-union were enrolled. The patients were divided in two groups: those treated with Ilizarov technique (Norm group) and those treated with Ilizarov technique combined with teriparatide injection (Teri group). Surgical duration, complication rate, bone healing status, clinical and functional outcomes were assessed according to the A.S.A.M.I. classification in the mean follow-up of 12 months. The subjective quality of life was assessed by the Short Form Survey (SF)-12.

Results Teri group showed less time wearing Ilizarov's frame ($p < 0.05$) than the Norm group and a statistical significance in the inter-rater reliability Cohen's k ($p > 0.05$) respect to Norm according the score between the bone healing and clinical outcome results. There was no statistically significant difference between the two groups in other parameters that were assessed.

Conclusion A benefit of teriparatide was found as adjuvant in the treatment of septic non-union.

Key words: bone regeneration, Ilizarov technique, teriparatide, tibia, limb salvage, osteomyelitis

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INTRODUCTION

Non-union is defined as a persistent failure of the healing process of fractures, generally after 6-8 months (1). This is often a delayed complication of fracture; the incidence of long bone non-unions has been estimated to 5-10% (1). Septic non-union is defined as absence of the bone healing process and concomitant infection of the fracture site for 6-8 months (2). Infected non-unions of tibia are a challenging clinical condition for both orthopaedic surgeons and patients. In this complex scenario it is possible to find recalcitrant infection, complex deformities, sclerotic bone ends, large bone gaps, limb shortening, and joint stiffness (2). A correct bone and soft tissue surgical debridement, associated with Ilizarov osteodistraction technique, is commonly used in these cases (3), as reported in war surgery (4,5).

Although the pathophysiology of non-union is largely unknown, certain risk factors have been well reported. Mechanical causes like low-grade fracture stability or repeated manipulations of a fracture may delay the healing process. Systemic risk factors like diabetes, smoking, osteoporosis, and estrogenic deficiency reduce the chance of recovery (6).

Recently the use of bone-regenerating adjuvant drug and bioengineering therapy is of growing importance (6). One of these innovative therapeutic possibilities is the use of teriparatide, a recombinant human parathyroid hormone, that was proposed for the treatment of postmenopausal osteoporosis (7).

Several studies reported the role of teriparatide on bone tissue (6-8). A randomized double-blinded study tasted its beneficial effects on fracture repair in in postmenopausal women with fractures of the distal radius; the authors noticed a reduced time of fracture healing in a group of patients treated with 20 ηg/day of teriparatide compared with placebo (8).

The aim of this study was to analyse the role of teriparatide combined with the Ilizarov oestrogenic distraction and to compare this therapeutic option with the isolated Ilizarov technique.

PATIENTS AND METHODS

Patients and study design

Skeletally mature patients who enrolled in this retrospective study were operated between 2006 and 2018. A total of 112 tibial non-unions were treated. Forty patients aged between 18 to 65 years, with the Type C of Association for the Study and Application of the Method of Ilizarov (ASAMI) non-union (9) were enrolled in the study. Other 72 patients were excluded according the exclusion criteria: concomitant systemic disease patients, acute infection, type A and B ASAMI of bilateral tibial non-union.

The patients were divided in two groups: 20 patients treated with Ilizarov Technique (Norm group) and those treated with Ilizarov technique combined with teriparatide injection (Teri group).

All patients were assessed in a multidisciplinary clinic, comprising orthopaedic and plastic surgeons and infectologists. Antibiotic therapy was stopped at least 14 days before the surgery to aid microbiologic diagnosis.

The Non-Union Scoring System (NUSS) (1) was used to classify the non-union in retrospective mode1.

The study was performed according to the criteria set by the Helsinki Declaration, every patient read, understood and signed a dedicated informed consent.

Clinical, surgical (postoperative complication rate, surgical duration) and radiological outcomes were retrospectively evaluated at a minimum 12-month follow-up after the Ilizarov frame removal.

Bone tissue and functional outcomes were evaluated according to the ASAMI classification, while the Short Form 12 Health Survey (SF-12) was used to assess the subjective quality of life after surgery (9-10).

Azienda Sanitaria Locale (ASL) Lecce/Italy Ethical Committee approved this research.

Methods

Surgical technique. Firstly, the accurate evaluation of fracture stability was performed: the non-union was defined “stiff” if there was an angular bending of less than 7° and/or axial movement of less than 5 mm. Adequate surgical debridement (Figure 1, Figure 2) until the healthy and bleeding bone tissue was evident. The medullary canal was reamed.

Bone compression was performed in cases of mobile non-unions with segmental bone loss af-

Figure 1. 45-year-old male with surgical wound complication at 4 months after proximal tibial fracture treated with straight plate and screws, in another hospital A,B) Cutaneous defect presentation; C,D) Radiographs preoperative; E) Bone resection; F) implant of modular external fixator; G) for healing the skin; H,I) implant of Ilizarov's frame; J,K) docking point; L) good clinical and radiographic results according to ASAMI classification; M) cutaneous defect healing (Falzarano G. 2014)

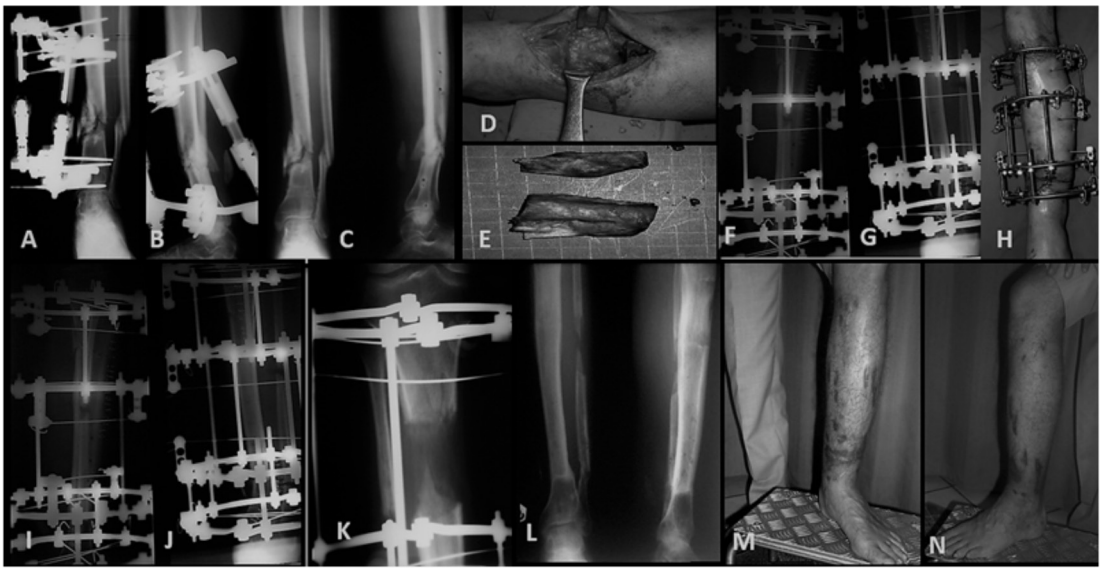

Figure 2. 42-year-old male. A, B) open fracture according Gustilo Anderson classification type IIIB of the distal leg extremity treated with external fixator frame; C) After 6 months there was Cierny Mader IV A: widespread bone marrow and cortical infection with multiple seizures on the bone periphery but free from systemic pathologies or severe local impairment; D, E) Bone resection; F,G,H) Implantation of the lizarov's frame; I, J) Proximal corticotomy after 4 weeks; K) X-ray of regenerated bone after 3 weeks of teriparatide injection; L) X-rays after removed of Ilizarov's frame shows an excellent regeneration is an excellent result according to ASAMI classification; M, N) Excellent clinical and aesthetic results (Meccariello L. 2016)

ter excision. In cases of severe posttraumatic deformities, the fibular osteotomy was performed before the surgical reduction and compression of the fracture. In all patients, skin suture was performed, either directly or using local or free microvascular muscle flaps to restore a healthy soft tissue envelope.

Postoperative protocol. In the postoperative period, the bone transport technique was performed. Segment transport started at 7 days after surgery (1 mm/day).

The patients were treated with a standard postoperative antibiotic therapy (vancomycin and meropenem) and then switched to a culture-specific

antimicrobial therapy until the normalization of the inflammatory markers in blood test. Knee and ankle joints mobilization started on the second day after surgery and early full-weight-bearing was encouraged. Radiographs were performed 2 weeks during the distraction period and monthly during the consolidation period. In the Teri group, the subcutaneous injection of teriparatide 20 μg/day for three months was applied, when starting from the contact of the docking-site.

The Ilizarov frame was removed when a solid docking-site union and a minimum of three complete cortices regeneration was evident at x-rays.

Statistical analysis

Continuous variables were expressed as the mean±standard deviation (SD) as appropriate. The Shapiro-Wilk normality test was used to evaluate the normal distribution of the sample. The t test was used to compare continuous parameters. The Fisher exact test were used to compare Categorical variables (in the groups smaller than 10 patients). A correlation between preoperative radiographic indices and lowering effect in patellar height was calculated using the Pearson's correlation. The study sample size was considered sufficient to evaluate a difference in post- to pre-operative measurements greater than 0.5 SD units with power >80%.

The reliability and validity of the correlation between bone regenerate/bone healing and X-rays were determined by the Cohen's kappa (k). Statistical significance was set at $p < 0.05$.

RESULTS

The two study groups reported no statistically significant differences in age, gender, mean surgical time, bone resection, bone transport time, External Fixation Index (Table 1).

The mean follow-up was 1.7 years (±0.6; range 1-5) in the Norm group and 1.6 years (±0.5; range 1-5) in the Teri group. The mean surgical time was 230.2 (±28.8; range 164-284) minutes in the Norm group and 230.6 (±28.7; range 162-283) in the Teri group. The average bone resection was 9.2 (±3.75, range 5.2-15.3) cm in the Norm, while 9.1 (±9.22 range 5.2-15.2) in the Teri group ($p>0.05$). The mean bone transport time was 79.4 (±8.34; range 44-92) days in the Norm group while in the Teri group it was 79.7 (±8.30; range 42-90) days. No statistically significant differences were reported in the complication rate. The mean treatment duration with Ilizarov frame was 19.24 months (±10.34; range 9–32) in the Norm, while 16.24 months (±7.83; range 9–31) in the Teri group ($p<0.05$) (Table 2).

Table 1. Description of the Norm and Teri groups

Characteristic	No (%) of patients in the group		p
Description of Population	**Norm**	**Teri**	
Number of patients	20	20	1.000
Average age (SD) (years)	39.55 (±4.10)	39.84 (±4.11)	0.678
Age range (years)	22-65	23-65	0.831
Gender (ratio M:F)	9 (18:2)	9 (18:2)	1.000
Type of fracture			1.000
Closed	5 (25.00)	5 (25.00)	
Open	15 (75.00)	15 (75.00)	
Type of open fracture according Gustilo Anderson			
I	1 (6.67)	1 (6.67)	1.000
II	3 (20.00)	3 (20.00)	1.000
IIIA	5 (33.33)	5 (33.33)	1.000
IIIB	5 (33.33)	5 (33.33)	1.000
IIIC	1 (6.67)	1 (6.67)	1.000
Average time (SD) from fracture to chronic infection (range) (years)	3.54 (±1.24; 2-8)	3.87 (±1.26; 2-8)	0.598
Type of non-union according ASAMI classification			
C	20 (100)	20 (100)	1.000
Type Cierny Mader osteomyelitis's classification			
Stage 3A	4 (20)	4 (20)	1.000
Stage 3B	6 (30)	5 (25)	0.637
Stage 4A	5 (25)	5 (25)	1
Stage 4B	5 (25)	6 (30)	0.637
Average non-union scoring System (SD; Range)	69.32 (±3.40; 51-84)	69.72 (±3.39; 51-84)	0.053

SD, standard deviation; ASAMI, Application of the Method of Ilizarov; The reliability and validity of the correlation between bone regenerate/bone healing and X-ray was determined by the Cohen's kappa (k)

The Teri group had a statistical significance in the inter-rater reliability Cohen's k ($p>0.05$) respect to the Norm according the score between the bone healing and clinical outcome results (Table 2).

According to the ASAMI classification the same results in both groups were found (Table 3): excellent in eight (40%), good in six (30%), moderate in six (30%) patients; no patients with poor result. At 12-month follow-up the SF-12 in the Norm group was 73.6 (range 62-90), and in the Teri group, the SF-12 was 76.7 (range 64-90) ($p>0.05$). At the moment of total weigh bearing the SF-12 score in the Norm group was 66.3 (range 40-84), while in the Teri group it was 66.4 (range 40-84), $p>0.05$. At 12 months after Ilizarov frame removal SF-12 was 82.9 (range 64-92) in the Norm group, while it was 82.3 (range 64-92) in the Teri group ($p>0.05$).

Table 2. Results and outcome in the Norm and Teri groups

Characteristic	Norm group	Teri group	p
The mean follow-up after removal of the Ilizarov's apparatus (SD; range) (years)	1.7 (±0.6; 1-5)	1.6 (±0.5; 1-5)	0.05
Average surgical time (SD; range) (minutes)	230.2 (±28.8 164 -284)	230.6 (±28.71; 62 -283)	0.05
Average bone resection in cm (SD; range) (cm)	9.2 (±3.75; 5.2-15.3)	9.1±9.22 (5.2-15.2)	0.05
Bacteriological cause of infection (No; %)			N/A
Methicillin-resistant *Staphylococcus aureus*	5 (25)	5(25)	
Staphylococcus aureus	2 (10)	2 (10)	
Pseudomonas spp.	3 (15)	3 (15)	
Enterobacter cloacae	2 (10)	2 (10)	
Escherichia coli	3 (10)	3 (10)	
Klebsiella spp.	1 (5)	1 (5)	
Enterococcus faecalis	1 (5)		
Acinetobacter baumanii		1 (5)	
Streptococcus spp.	1 (5)	1 (5)	
Proteus mirabilis	1 (5)		
Morganella morganii		1 (5)	
Enterococcus sp.	1 (5)	1 (5)	
Average time of bone transport took in days (SD; range)	79.4 (±8.34; 44-92)	79.7 (±8.30; 42-90)	0.05
Average External Fixation Index (SD; range) (months/centimetres)	0.97±0.47 (0.44–1.76)	0.94±0.53 (0.36–1.80)	0.05
Type of complication			
Blood loss	1215±160.30 mL	1218±159.28 mL	0.0638
Intra operative fracture	0	0	1.000
Loosening of wires or pins	2 (10)	2 (10)	1.000
Limb shortening (from 1 to 2.9 cm)	6 (30)	6 (30)	1.000
Local skin inflammation	6 (30)	6 (30)	1.000
Docking point skin retraction	3 (15)	3 (15)	1.000
Retard to consolidation of bone regenerate	4 (20)	4 (20)	1.000
Average correlation between bone regenerate-bone healing/ X-rays	k=0.815755 ±0.104632	k=0.817252 ±0.056518	p<0.042
Average time for removal of Ilizarov's frame (SD; range) (months)	19.24±10.34 (9–32).	16.24± 7.83 (range 9–31)	0.036

N/A, non-applicable

Table 3. Outcome of patients in the Norm and Teri groups according to the application of the Method of Ilizarov (ASAMI) classification

Outcome	No (%) of patients in the group		p
	Norm	Teri	
Excellent: Union, no infection, deformity <7°, limb length discrepancy (LLD) <2.5 cm	8 (40)	8 (40)	1.000
Good: Union plus any two of the following: absence of infection, deformity <7°, (LLD) <2.5 cm.	6 (30)	6 (30)	1.000
Fair: Union plus any one of the following: absence of infection, deformity <7°, LLD <2.5 cm.	6 (30)	6 (30)	1.000
Poor: Nonunion/refracture/union plus infection plus deformity >7° plus LLD >2.5 cm	0	0	1.000

LLD, Limb length discrepancy;

DISCUSSION

The main finding of the study was a benefit of teriparatide as adjuvant in the treatment of septic non-union. There was a difference in time to remove Ilizarov frame between two groups and a statistically significant correlation in Bone Regenerate-Bone Healing/X-rays.

In large patients' cohorts, 4.9% of non-union rate (scaphoid 15.5%, tibia 14% and femur 13.9%) were reported (11). Therefore, all strategies that help to reduce healing time with faster resumption of work and activities not only improve medical outcome for the patient, they also reduce the financial burden in fracture and non-union patients (11).

Several studies investigating the effect of parathyroid hormone in accelerating bone formation in animal models found an increase of bone mineral density (BMD) by 24–33% and mechanical stiffness and load to failure increased by over 50% (12).

In humans, daily subcutaneous injection of teriparatide has been used to accelerate bone-healing process. Patients treated with teriparatide healed in 7.8 weeks, while the control group without teriparatide injection healed in 12.6 weeks and reported worse functional outcomes (13). Another study analysed 34 patients with osteoporotic distal radius fracture, treated with 0.20 mg teriparatide who healed in 7.4 weeks, whereas the control group healed in 9.1 weeks. Clinical scores were better in teriparatide patients and no difference in grip strength was reported (8). Teriparatide is an anabolic drug that can help bone healing, but there is no consensus on the clinical indication.

Investigating 16 cases of septic tibial bone defects that underwent bone segment transport and 8 weeks of treatment with daily subcutaneous 0.20 μg teriparatide injections followed by 8 weeks with no treatment, or 8 weeks with no treatment followed by 8 weeks with daily subcutaneous 0.20 μg teriparatide injection, the authors noticed that teriparatide during the consolidation phase doubled the mineralization rate of the regenerate, compared to no treatment (14). Teriparatide use should be limited to selected patients presenting severe forms of osteoporosis, presence or history of multiple fractures, exposed high risk for subsequent fractures, or patients with osteoporosis resistant or intolerant to other specific therapies (15).

Abuomira et al. compared Taylor spatial frame trifocal and bifocal techniques for the treatment of seven segmental bone defects of the tibia; the docking site ossification phase was gradually stimulated (16). The simple compression procedure requires less invasive surgery and is probably less demanding and more cost-effective in short transports (10,16).

In our study, teriparatide aimed to accelerate the bone healing and remove the Ilizarov frame faster. The 3-8 month teriparatide treatment (20 μg/day) helps the non-unions consolidation in long bone non-unions as well as in the animal models (12, 17-20). The efficiency of this treatment seems to be associated with patient comorbidities comparing to the isolated Ilizarov technique (17).

The limited number of enrolled patients and the retrospective nature of the study were the most important study limitations.

In conclusion, the use of teriparatide off-label has a positive and additive effect when combined with the Ilizarov technique. Positive effect of teriparatide on fracture healing is well-documented, however, further studies are needed to confirm these promising hypotheses.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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