Injury, Int. J. Care Injured 50 (2019) 1478–1482

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Daily subcutaneous Teriparatide injection increased bone mineral density of newly formed bone after tibia distraction osteogenesis, a randomized study

Frithjof Wagner[a], Werner Vach[d], Peter Augat[b], Patrick A. Varady[b], Stephanie Panzer[c], Silke Keiser[b], Henrik Eckardt[d,*]

[a] Department of Trauma, BG Unfallklinik Murnau, Murnau, Germany
[b] Institute for Biomechanics, Paracelsus Medical University, Salzburg, Austria
[c] Department of Radiology, BG Unfallklinik Murnau, Murnau, Germany
[d] Department of Trauma, Basel University Hospital, Basel, Switzerland

ARTICLE INFO

Article history:
Accepted 2 June 2019

Keywords:
PTH
Tibia
Bone defect
Bone regeneration
Bone healing
Distraction osteogenesis

ABSTRACT

Long bone defects are often treated by bone segment transport with the Ilizarov method requiring months spent with fixator mounted until bony consolidation of the newly formed bone. Shortening of consolidation would allow earlier fixator removal and earlier return to work. In pre-clinical studies parathyroid hormone, increased bone mineral density and mechanical properties of regenerate bone formed during distraction osteogenesis. Clinical studies showed that Teriparatide accelerated fracture healing in patients with osteoporotic fracture of the pelvis, hip, wrist and shoulder. We hypothesized that rhPTH(1-34) (Teriparatide) administered to patients who had undergone distraction osteogenesis, would increase mineralization of the regenerate formed during the consolidation phase.

Sixteen patients with tibial defects after infection, underwent bone segment transport and at the time of docking the transport segment, were randomized to 8 weeks treatment with daily subcutaneous 0.20-μg Teriparatide injection followed by 8 weeks with no treatment, or to 8 weeks with no treatment followed by 8 weeks with daily subcutaneous 0.20 μg Teriparatide injection. Bone mineral density (BMD) of the regenerate was measured at the time of docking, 8 weeks after docking and 16 weeks after docking with DEXA. Functional evaluation was performed after one year. The design was a cross-over study.

Overall BMD increased 0.14 g/cm^2 in 8 weeks without treatment and 0.33 g/cm^2 under Teriparatide treatment. After adjustment for a potential phase difference, 8 weeks of Teriparatide treatment led to an additional 0.19 g/cm^2 BMD increase (95%-CI:[0.11,0.28], $p < 0.001$). The ratio of the BMD increase between the two treatments was 0.33/0.14 = 2.43 (CI: [1.21,3.65]).

Teriparatide treatment during the consolidation phase of distraction osteogenesis doubled the mineralization rate of the regenerate when compared to no treatment.

Introduction

Bone loss after tumor or infection is often treated by bone segment transport, a process where long bones, stabilized by an external or internal fixator, are first osteotomized and then lengthened at a rate of 0.5 mm–1 mm each day. The metaphysis is osteotomized and a controlled series of micro fractures through the callus of the osteotomy gap followed by distraction of the gap produces competent bone with properties identical to parent bone [1]. After lengthening is completed, consolidation of the newly formed bone requires continuation of external or internal fixation until the bone can be fully loaded. On average the adult patient spends 35 days with the bone stabilized in a fixator for every 1 cm elongation [2]. I.e. 10 cm of lengthening requires 100 days of lengthening and 250 days of consolidation, thus almost one year of fixation. Shortening the consolidation phase by even one month would reduce patient morbidity, increase patient satisfaction and allow earlier return to work.

Teriparatide (rhPTH(1-34)) is the active fragment (1-34) of endogenous human parathyroid hormone (1-84)(PTH). Once-daily administration of PTH increases apposition of new bone on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In an experimental

* Corresponding author at: Department of Trauma, Basel University Hospital, Basel, Switzerland.
E-mail address: henrikeckardt@gmail.com (H. Eckardt).

https://doi.org/10.1016/j.injury.2019.06.001
0020-1383/

femoral bone lengthening model in rats, PTH increased callus size and strength [3], and in an experimental tibia lengthening model in rabbits PTH increased biomechanical properties, bone mineral content and callus size [4]. In a more recent and similar study, biomechanical properties of the regenerate increased more rapidly in rabbits receiving intermittent PTH, and after 10 weeks there was no longer any difference between the control group and the PTH treated group [5]. There are no human studies investigating the effects of PTH treatment during bone lengthening. We are aware of 11 controlled clinical studies investigating the effect of Teriparatide on fracture healing after osteoporotic fracture. There were 2 pelvic fracture studies, 2 spine, 3 proximal femur, 1 distal femur, 2 wrist and 1 shoulder fracture study. In all studies, daily subcutaneous injections of 20 μg Teriparatide was used except in one study where daily injections of 20 μg were compared to 40 μg injections. Duration of the therapy was 4 weeks to 11 months. In all but one study, Teriparatide either increased fracture healing, reduced pain or improved functional performance [6]. Teriparatide (rhPTH(1-34)) is registered in all EU countries for the prevention of osteoporosis in postmenopausal women and in men, but its use to accelerate fracture healing still is experimental. We hypothesized that Teriparatide treatment of patients undergoing bone lengthening of the tibia after infection would lead to increased bone mineralization in the zone of newly formed bone during the consolidation phase of distraction osteogenesis.

Methods

The study was designed as an open randomized cross over study with two treatment arms and two treatment phases. The treatments were either Teriparatide (PTH) or no Teriparatide (No PTH). The first treatment phase (Phase 1) started at the time of docking and ended 8 weeks later and the second phase (Phase 2) started 8 weeks after docking and ended 16 weeks after docking.

Included were patients older than 25 years with tibial bone defects due to bone resection after osteomyelitis who had undergone bone segment transport with a circular frame at our clinic. After successful bone transport and docking, patients were screened and 16 patients were included after informed consent.

Exclusion criteria were the following: Diabetes mellitus, hyper or hypoparathyroidism, hypercalcemia at time of inclusion, presence of urolithiasis, elevated alkaline prosphatase, Severe renal failure diagnosed by serum Creatinine >2 mg/dl or GFR (according to MDRD) below 30 ml / min / 1,73m2, liver disease, Mb Paget, known allergy to Teriparatide, history of any malignant or neoplastic disease, prior radiation therapy of the skeleton, persistent osteomyelitis, severe deformity after distraction, smoking, alcohol or morphine dependence, medication affecting bone metabolism within the last 2 years, pregnancy or breast feeding, female and not willing to use adequate contraception.

Patients were randomized to either treatment arm 1 (PTH/No-PTH) or treatment arm 2 (No-PTH/PTH).

Patients in the PTH/No-PTH group received Teriparatide 20 μg/day daily as subcutaneous injections for 8 weeks after docking followed by 8 weeks without Teriparatide. Patients randomized to No-PTH/PTH received no Teriparatide in the first 8 weeks after docking and received Teriparatide 20 μg/day daily subcutaneous between week 8 and week 16. Randomization took place 2 days after successful docking by drawing of a sealed envelope. No stratification or blocking procedures were performed. Random numbers were generated electronically by an open random numbers calculator.

The primary outcome variable was the BMD of the bone regenerate, which we assessed at baseline, after 8 weeks (Phase 1), and after 16 weeks (Phase 2). The primary endpoint was the BMD increase between start and end of treatment.

Secondary endpoints included measures of physical function 12 months after docking when the regenerate had consolidated. We assessed the function of adjacent joints using the American Orthopedic Foot and Ankle Society (AOFAS) ankle score and the Lower Extremity Functional Scale (LEFS). In addition, the "Timed Up and Go" (TUG) test evaluated mobilization ability.

Bone mineral density (BMD)

Areal BMD was obtained from dual X-ray absorptiometry (DXA, Lunar Prodigy Advance, GE Helthcare, Munich, Germany). A scout scan was performed and a rectangular region of interest was sketched that would include the complete region of the regenerate (Fig. 1). The region had about 0.5 mm distance from both bone ends encompassing the whole bone regenerate and excluding all metal present from the external fixator system. This region was reproducible and was used for repeated measurements within the same patient. The BMD was subsequently calculated as bone mineral content of the region divided by the area of the region measured in g/cm^2.

Functional scores

American Orthopedic Foot and Ankle Society (AOFAS) foot and ankle score is a clinician reported score to assess the function of the ankle joint through a mixture of 9 questions covering 3 categories: pain (40 points), function (50 points) and alignment (10 points). It gives a total score from 0 to 100, with higher scores indicating better function and satisfaction. [7]

The Lower Extremity Functional Scale (LEFS) is a 20-item region-specific patient reported measure where the degree of difficulty in performing different physical activities due to problems in the lower extremities are rated on a 5-point scale.

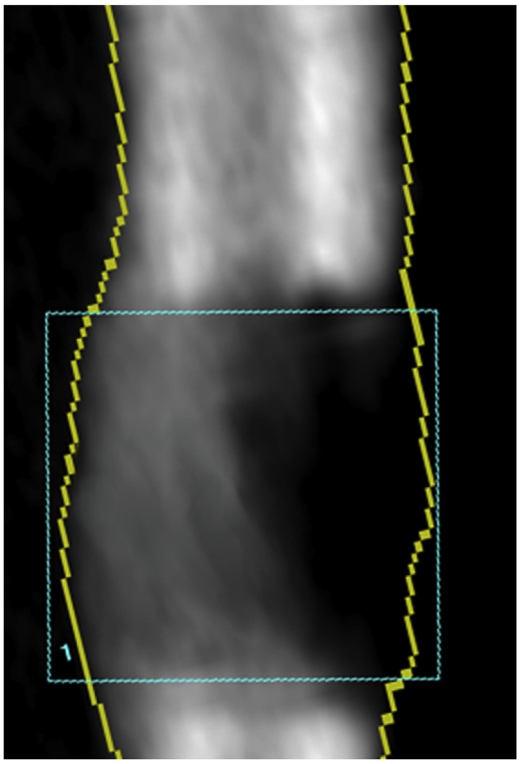

Fig. 1. Measurement of BMD. The quadrangle marked the region of interest and BMD was calculated as bone mineral content of the green quadrangle as measured with DEXA divided by the area of the region. The cortex of the bone is marked with the interruped line.

Table 1
Shows the number of patients receiving PTH treatment or No-PTH treatment in phase 1 (0–8 weeks) and phase 2 (8–16 weeks) and the number of patients with available DEXA measurements at docking (week 0), 8 weeks later (week 8) and 16 weeks later (week 16).

	PTH / No-PTH group	No-PTH / PTH group
Week 0	PTH: 8 patients DXA: 7 patients	No-PTH: 8 patients DXA: 6 patients
Week 8	No-PTH: 8 patients DXA: 7 patients	PTH: 7 patients DXA: 7 patients
Week 16	DXA: 5 patients	DXA: 7 patients (including 2 patients not receiving PTH)

It gives the total score from 0 to 80, with higher scores indicating better function. [8]

For the timed up and go test (TUG) we timed the duration of the following procedure: the patient sat on a chair, rose, walked 4 m, turned, walked back and seated again. [9]

Finally we calculated the bone healing rate, which is the time spent with the fixator mounted on the leg divided by the length of the newly formed bone.

Statistics

For the sample size calculation we leaned on that the bone mineralization rate of the lengthened bone is relatively constant and complete bone mineralization occurs after 6 months. A 25% BMD increase of the bone mineralization rate will thus shorten a 6-month consolidation phase in human by at least 1 month, which we considered clinically relevant. We thus set the minimal relevant difference equal to a 25% BMD increase of the bone regenerate, standard deviation of BMD in a pilot evaluation was 18%, and with the power set to 0.8 and the significance level equal to 0.05, the necessary sample size equaled 16 patients when using a two-sample *t*-test to compare the relative increase in BMD between two groups. Due to the cross-over design, we can actually expect a larger power.

The data was analyzed by assessing the absolute change in BMD within phase 1 and within phase 2 for each patient and considering mean values stratified by phase and group. The overall effect was assessed by pooling the data from both phases stratified by treatment. The significance of the overall effect was determined by considering a mixed model with patient as random effect and treatment and phase as fixed effects. The inter-patient variation in treatment effect was assessed by a mixed model applied to the raw data with time and phase as fixed effects and patient and treatment (within patient) as random effects.

Data was analyzed with a "per-protocol" analysis at the phase level as the primary approach and an "as-randomized" analysis as secondary approach. Phases in which the BMD change could not be determined due to missing BMD values were ignored in the analysis.

Study approval was obtained by the Ethical Committee of Bavarian Medical Board, Germany (Reg.Nr. 08041). The study protocol was registered at the European Union clinical trials register (EudraCT 2008-000592-24). Written informed consent was obtained from each patient participating in this study.

Results

Between 2009 and 2013, 16 Patients were included in the study and randomized for treatment. Fourteen were male and 2 females. Age ranged from 26 to 57 years. All patients had bone resected due to osteomyelitis after fracture. The mean bone defect was 61 mm (range 35–127 mm). Six patients encountered complications during distraction necessitating ring corrections, re-osteotomy by premature consolidation, soft tissue revisions or antibiotics.

Table 1 depicts the completeness of our data. Two patients in the No-PTH/PTH arm did not receive PTH treatment due to organizational difficulties, and hence contribute only with the BMD change under phase 1 in the primary analysis. DEXA scans were not performed in all patients such that only 23 instead of 32 BMD changes could enter the primary analysis.

Fig. 2 shows the BMD changes in phase 1 and phase 2. The average changes are shown in Table 2 stratified by group and phase and rearranged by Teriparatide treatment and phase. Pooled over both groups we observed an average increase of 0.14 g/cm^2 in 8 weeks without treatment and an average increase by 0.34 g/cm^2 under Teriparatide treatment. After adjustment for a potential phase difference, we conclude that 8 weeks of Teriparatide treatment leads to an additional 0.21 g/cm^2 increase in BMD (95%-CI:[0.13 g/cm^2, 0.30 g/cm^2], $p < 0.001$). The ratio of the BMD increase between the two treatments was 0.34/0.14 = 2.55 (CI: [1.20,3.91]). When using a random effects model to assess the inter-patient heterogeneity of the treatment effect, we observed an inter-patient standard deviation of 0.23 (95% CI: [0.15,0.34], $p < 0.001$). The "as-randomized" analysis indicates an average BMD increase of 0.31g/cm^2 in the PTH treated group, and a treatment difference of an additional 0.17 g/cm^2 increase (95%-CI: [0.06 g/cm^2, 0.29 g/cm^2], $p = 0.004$). At the clinical control 12 month after docking, 14 patients were available for functional assessment. The ring fixator had been removed in all 14 patients and all were fully weight bearing. The regenerated bone had radiographically a normal appearance but in one patient, the

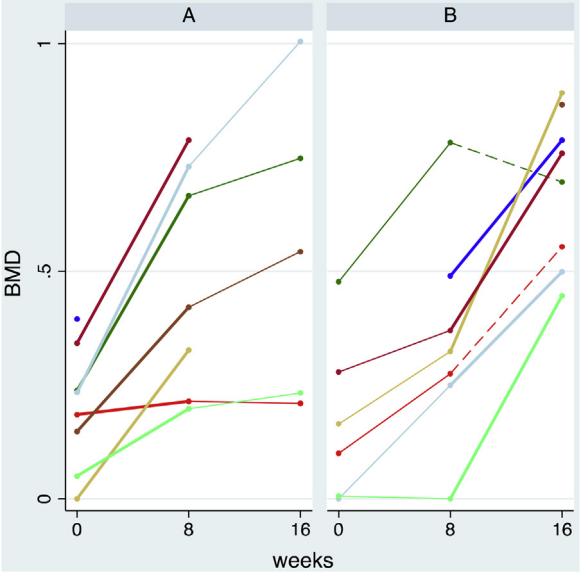

Fig. 2. The BMD measurements of the 16 patients included in this study. The unit of BMD is g/cm^2. Bold solid lines indicate a phase with PTH treatment, thin solid lines phases with No-PTH treatment. The dashed lines indicate the two patients who discontinued treatment and whose change in phase 2 did not enter the primary analysis.

Table 2
BMD increase (mean value ± standard deviation) and available sample sizes for the two treatment groups and phases and the comparison between PTH treatment and No-PTH treatment combined for both phases.

BMD in g/cm^2	Phase 1	Phase 2		Phase 1 & 2
PTH/No-PTH	0.31±0.17 (N = 7)	0.10±0.11 (N = 5)	PTH	0.33±0.16 (N = 11 or 12)
No-PTH/PTH	0.16±0.11 (N = 6)	0.38±0.14 (N = 4 or 5)	No-PTH	0.14±0.11 (N = 11 or 12)

docking site was not consolidated radiographically. The mean Lower Extremity Functional Scale (LEFS) was 52 (range 15–80). The TUG showed that 7 patients were freely mobile (t < 10 s) and 7 patients were mostly independent (10 s < t < 20 s). The AOFAS foot and ankle score was available in 11 patients with a mean of 56 (range 27–97). The bone healing rate of the regenerate could not be determined in one patient due to re-osteotomy; in the remaining 15 patients the mean bone healing rate was mean of 50.7 days/cm (range 19.7–108.7 days/cm).

Discussion

In this clinical experiment, daily subcutaneous injections of 0.20 μg Teriparatide increased BMD of the regenerate formed in patients after tibial lengthening and docking of the regenerate. Our results suggest that Teriparatide treatment may – on average - more than double the mineralization rate of the regenerate during the consolidation phase. We could observe this effect not only on average, but also for the majority of individual patients. However, there was a statistically significant variation in the individual treatment effects.

BMD has been recognized as a reliable surrogate for the mechanical strength of regenerating bone during limb lengthening procedures. Saran measured BMD of the regenerate during the consolidation phase in 26 patients and found the BMD of the regenerate to be a strong predictor for safe removal of the fixator after bone lengthening. Once BMD had plateaued and less than 10% increase per month was seen, the fixator could be removed [10]. Maffuli found that once BMD of the regenerate reached 70% of the original bone, the fixator could be removed without the risk of refracture [11]. Given that BMD of the regenerate can guide the time to fixator removal, and that BMD continues to increase under Teriparatide treatment, daily subcutaneous Teriparatide injection during the consolidation phase could potentially reduce the time to safe removal of the fixator.

There are no previous studies investigating an effect of parathyroid hormone in humans undergoing distraction osteogenesis. Parathyroid hormone has been used in experimental distraction osteogeneses to accelerate bone formation in mouse, rats and rabbits. Intermittent daily PTH treatment increased the BMD by 60% and the load to failure in torsion to failure test in rabbits undergoing tibia lengthening [4]. In rats undergoing femoral lengthening, intermittent PTH treatment every second day increased BMD by 24–33% and the mechanical stiffness and load to failure increased by over 50% [3].

In humans, daily subcutaneous injection of 0.20 μg Teriparatide has been used to accelerate fracture healing in osteoporotic fractures in several studies. In an observational study in patients with conservatively treated insufficiency fractures of the sacrum 21 patients received Teriparatide treatment and 44 patients recruited at a different hospital served as untreated controls. Patients treated with Teriparatide healed in 7.8 weeks and untreated patients healed in 12.6 weeks and had more pain and worse functional scores [12]. 78 patients with osteoporotic femoral neck fracture treated with screw fixation of the fracture received Teriparatide treatment and 81 operated patients served as control. The Teriparatide group had better functional score after 12 months but no difference in time to union or pain control was seen [13]. 86 patients with pertrochanteric fracture stabilized with hip screw or intramedullary nail and treated with Teriparatide had faster mobilization with less pain after 12 and 18 weeks than patients receiving Risedronate and no Teriparatide, but no difference in time to union was seen [14]. 34 Patients with osteoporotic distal radius fracture were treated with 0.20 μg Teriparatide and healed radiologically in 7.4 weeks, whereas 34 control patients healed in 9.1 weeks. Pain scores were lower in Teriparatide treated patients, but grip strength was not different [15]. 20 patients with proximal humeral fractures that were treated conservative and received Teriparatide had no difference in time to union and functional scores in comparison to patients not receiving Teriparatide injections [16]. The only clinical study in non-osteoporotic fractures was a clinical trial testing the effect of daily Teriparatide injections on implant fixation after total knee replacement in 50 patients. There was no effect on implant migration as measured with radiosterometric analysis one year postoperative [17]. Thus, several studies suggest a role for Teriparatide in human traumatology as an anabolic drug that increase bone healing, but the indication is not clear.

The bone healing index (the time spent with fixator mounted divided by the number of centimeter lengthening) was 51 days/cm (range 20–109 days/cm) in our study, which is a normal average for complex defect reconstruction but the range is very wide in our study. The functional result of the patients in our study is normal for patients with severe lower extremity trauma. The AOFAS foot and ankle score was 71.5 (range 41–82) which is better than the results obtained one year after operatively treated pilon fracture but worse than the results after osteosynthesis of a simple ankle fractures [18,19]. The Lower Extremity Functional Scale (LEFS) was 51 (range 15–80). For comparison, a cohort of below knee amputated patients reported LEFS equal to 41, which is worse than our group, and patients undergoing tibial defect reconstruction with Masquelet technique had LEFS equal to 53 [20]. As expected in a group of patient with age ranging from 26 to 57 years, the TUG showed good mobility and high independence. Our study was too small to compare the two phases of treatment (0–8 weeks vs 8–16 weeks after docking) or the functional results between the two treatment groups, hence we are not able to recommend whether Teriparatide treatment should be started immediately after docking or later. There are few reported side effects of the Teriparatide treatment in the studies above, and no patients in our study stopped Teriparatide injection due to side effects. Thus, Teriparatide treatment could start immediately after docking and could be continued until consolidation in order to optimize the effect.

Our study has several limitations. Most importantly, patients with bone defects after bone removal due to osteomyelitis constitute a rather heterogeneous patient population. There is often also soft tissue problem to be solved and typically, individualized treatment procedures are required. Healing of the bone defects is often hampered by repeated surgical interventions, defective soft tissue conditions and comorbidities. The heterogeneity was limited by rather stringent inclusion criteria. Although we were able to achieve our required sample size, the DXA analysis remained incomplete in 4 out of 16 patients due to technical and

organizational reasons. Furthermore, 2 out of 16 patients did not comply with the prescribed treatment and could not be fully used in the per protocol analysis. The incompleteness of the data, weakens the conclusions. In addition, we only applied Teriparatide treatment from week 0–8 or 8–16 after docking, whereas the consolidation phase after 60 mm bone transport normally takes 20–35 weeks. Whether we can extrapolate the results of the first 16 weeks treatment to the rest of the consolidation phase is uncertain. Finally, BMD is a surrogate for regenerate stability, although several clinical and experimental studies proved that BMD of the regenerate correlated well with regenerate stiffness [10,11].

In conclusion, Teriparatide treatment during the consolidation phase after distraction osteogenesis doubled the mineralization rate of the regenerate when compared to no treatment. This promising perspective has to be corroborated in further randomized trials, considering treatment with Teriparatide during the whole consolidation period and with primary endpoint being time of fixator removal or a direct measure of regenerate stiffness.

Conflict of interest

All authors confirm that they have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

Lilly Deutschland GmbH provided Teriparatide free of charge for patients included in the study but did not participate in planning, conducting or analysing the study or writing this manuscript.

The manuscript has been displayed to Eli Lilly Deutschland prior to submission.

References

[1] Aronson J. Limb-lengthening, skeletal reconstruction, and bone transport with the Ilizarov method. J Bone Joint Surg Am 1997;79(8):1243–58.
[2] Maffuli N, Fixsen JA. Distraction osteogenesis in congenital limb length discrepancy: a review. J R Coll Surg Edinb 1996;41(4):258–64.
[3] Seebach C, Skripitz R, Andreassen TT, Aspenberg P. Intermittent parathyroid hormone (1-34) enhances mechanical strength and density of new bone after distraction osteogenesis in rats. J Orthop Res 2004;22(3):472–8.
[4] Aleksyniene R, Thomsen JS, Eckardt H, Bundgaard KG, Lind M, Hvid I. Parathyroid hormone PTH(1-34) increases the volume, mineral content, and mechanical properties of regenerated mineralizing tissue after distraction osteogenesis in rabbits. Acta Orthop 2009;80(6):716–23.
[5] Ohata T, Maruno H, Ichimura S. Changes over time in callus formation caused by intermittently administering PTH in rabbit distraction osteogenesis models. J Orthop Surg Res 2015;10:88.
[6] Kim SM, Kang KC, Kim JW, Lim SJ, Hahn MH. Current role and application of teriparatide in fracture healing of osteoporotic patients: a systematic review. J Bone Metab 2017;24(1):65–73.
[7] Cook JJ, Cook EA, Rosenblum BI, Landsman AS, Roukis TS. Validation of the american college of foot and ankle surgeons scoring scales. J Foot Ankle Surg 2011;50(4):420–9.
[8] Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. Phys Ther 1999;79(4):371–83.
[9] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39(2):142–8.
[10] Saran N, Hamdy RC. DEXA as a predictor of fixator removal in distraction osteogenesis. Clin Orthop Relat Res 2008;466(12):2955–61.
[11] Maffulli N, Cheng JC, Sher A, Ng BK, Ng E. Bone mineralization at the callotasis site after completion of lengthening. Bone 1999;25(3):333–8.
[12] Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 2011;93(17):1583–7.
[13] Bhandari M, Jin L, See K, Burge R, Gilchrist N, Witvrouw R, et al. Does teriparatide improve femoral neck fracture healing: results from a randomized placebo-controlled trial. Clin Orthop Relat Res 2016;474(5):1234–44.
[14] Aspenberg P, Malouf J, Tarantino U, Garcia-Hernandez PA, Corradini C, Overgaard S, et al. Effects of teriparatide compared with risedronate on recovery after pertrochanteric hip fracture: results of a randomized, active-controlled, double-blind clinical trial at 26 weeks. J Bone Joint Surg Am 2016;98(22):1868–78.
[15] Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 2010;25(2):404–14.
[16] Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. Acta Orthop 2016;87(1):79–82.
[17] Ledin H, Good L, Johansson T, Aspenberg P. No effect of teriparatide on migration in total knee replacement. Acta Orthop 2017;88(3):259–62.
[18] Jansen H, Fenwick A, Doht S, Frey S, Meffert R. Clinical outcome and changes in gait pattern after pilon fractures. Int Orthop 2013;37(1):51–8.
[19] Van Schie-Van der Weert EM, Van Lieshout EM, De Vries MR, Van der Elst M, Schepers T. Determinants of outcome in operatively and non-operatively treated Weber-B ankle fractures. Arch Orthop Trauma Surg 2012;132(2):257–63.
[20] Zoller SD, Cao LA, Smith RA, Sheppard W, Lord EL, Hamad CD, et al. Staged reconstruction of diaphyseal fractures with segmental defects: surgical and patient-reported outcomes. Injury 2017;48(10):2248–52.