

PTH AND ALENDRONATE IMPROVE OSTEOTOMY HEALING IN AN OSTEOPOROTIC RAT MODEL

Toro, J; Tomin, E; Shore, B; Sull, A; Morr, S; Myers, E; Lane, JM

The Hospital for Special Surgery, New York, New York (lanej@hss.edu)

Introduction

Osteoporosis is a major health problem in older populations, and is directly related to the increased rate of fractures in the elderly. Additionally, both aging and osteoporosis are known to be frequently associated with decreased quality of fracture repair. A number of drugs have been developed for the prevention and treatment of osteoporosis. The most commonly prescribed class of drugs for this purpose are the bisphosphonates, which act by inhibiting osteoclast activity and subsequent bone resorption. Numerous clinical studies have shown that treatment with bisphosphonates results in increased bone mass and decreased fracture risk when compared with untreated control populations. Previous animal studies with bisphosphonates have shown increased callus size and bone mineral content when compared to controls; however callus remodeling and fracture line appearance are inhibited, and *in vivo* and post-mortem mechanical studies have not shown an increase in torsional stiffness related to callus size. While bisphosphonates appear to be relatively safe with respect to metaphyseal fracture healing, there is minimal clinical data on the effect of bisphosphonates treatment on diaphyseal fracture healing in the osteoporotic population.

Forteo® (recombinant human PTH) is the first commercially available drug with a demonstrated anabolic effect on bone in animals and humans. PTH enhances bone mass at all four levels: cancellous, endocortical, intracortical and periosteal. Intermittent dosing of PTH has been shown to increase callus volume and mechanical fracture strength in animal studies, and there is evidence to suggest that fracture healing may be accelerated in animals treated with PTH. Additionally, PTH can stimulate bone formation independent of resorption, and can restore cancellous and cortical bone volume in parathyroidectomized rats. It was hypothesized that pretreatment with bisphosphonates would (i) compromise fracture healing, (ii) that post-fracture treatment with PTH would produce superior results in fracture healing when compared to Alendronate-

treated animals or controls, and (iii) that PTH would reverse pretreatment inhibition of bone metabolism secondary to bisphosphonates therapy.

Material & Methods

One hundred and twenty-six Sprague-Dawley rats were used for this study. The rats were ovariectomized and randomly divided into two groups: Group 1 (n=63) received 10 µg/kg/week of Alendronate by subcutaneous injection, and Group 2 (n=63) served as controls (no pretreatment). Surgery was performed on all rats at eight weeks post-ovariectomy. At the time of surgery, the group that received pre-treatment with Alendronate (Group 1) was randomly divided into three groups: Group 1a (n=21) continued weekly injections with Alendronate, Group 1b (n=21) received daily injections with rhPTH (Forteo®) (10 µg/kg/day), and Group 1c (n=21) received no treatment; the rats that did not receive Alendronate pretreatment were randomly divided into the same three post-surgical treatment groups (groups 2a-c). Surgical technique involved an open femoral osteotomy with a Stryker saw at the mid-diaphyseal level. After anesthesia and preparation, a 3 cm skin incision was made over the lateral femur. The femur was exposed by separating the vastus lateralis and rectus femoris muscles, and an osteotomy was made using a Stryker micro saw through the mid-diaphysis of the femur. A smooth Kirschner wire (1.1 mm) was then inserted in a retrograde manner through the medullary canal at the osteotomy site, exiting through the greater trochanter. The osteotomy was then reduced by inserting the K-wire through the distal femoral diaphysis. All animals were euthanized six weeks after surgery. Samples were analyzed by two-factor analysis of variance (ANOVA) with interaction. Mechanical testing was performed in all samples in four point bending using an ELF 3200 high precision mechanical testing apparatus (Endura TEC, Minnetonka MN). Bending stiffness, failure moment and failure deflection was determined. Material properties were estimated based on bending results and cross-sectional

geometry. Osteotomy healing was evaluated by manual palpation, biomechanical testing, μ CT analysis and qualitative histology. Statistical analysis was done using χ^2 and two-factor ANOVA tests.

Results

At 6 weeks the osteotomized femurs were tested. The union rates for animals pre-treated with Alendronate were as follows: Group 1a – 82%, and Group 1b – 78%, ($p=0.021$) compare to Group 1c – 44%. For the rats that did not receive pretreatment (Group 2), the union rates were as follows: Group 2a and 2b – 56%, Group 2c – 41%. The μ CT analysis showed increased volume of callus formation in rats treated with Alendronate and PTH over untreated controls ($p<0.05$).

Estrogen deficient rats from the control group showed a 59% nonunion rate at 6 weeks. Those rats that received pharmacologic intervention before osteotomy presented with a non union rate of 54% statistically insignificant compare to the control group.

Intervention with either Alendronate or PTH was statistically significant for all osteotomized samples after mechanical testing.

Mechanical results from the osteotomized callus evidenced homogeneous results non-dependable on the pharmacological intervention. Also, at six weeks the osteotomized callus samples demonstrated 30 % of bending stiffness compared to the non osteotomized side.

More important, Estrogen deficient rodents that received Alendronate or PTH did decrease the rate of nonunion compared to those estrogen deficient rats that both received Alendronate before osteotomy that was stopped after intervention or the control group. (table. 1)

Conclusions

In the setting of Estrogen deficient osteoporotic rat model, at 6 weeks, pretreatment with Alendronate and post treatment either with Alendronate or PTH prevented from the development of nonunion compared to the control group.

Pretreatment with Alendronate did not inhibit osteotomy healing, but prevents the development of nonunion when continued after surgical intervention in the estrogen deficient rat model. Comparable union rates results were evidenced by the use of PTH or Alendronate after osteotomy in both Alendronate pretreated group animals even though the pharmacological mechanism of action is known to be different.

In the osteoporotic animal model both PTH and Alendronate are enhancers of osteotomy healing.

*This study was supported by a grant of the Orthopaedic Trauma Association and the AO Research Fund.

Table 1.

