

PTH therapy reverses radiation induced non union and normalizes radiomorphometrics in a murine mandibular model of distraction osteogenesis

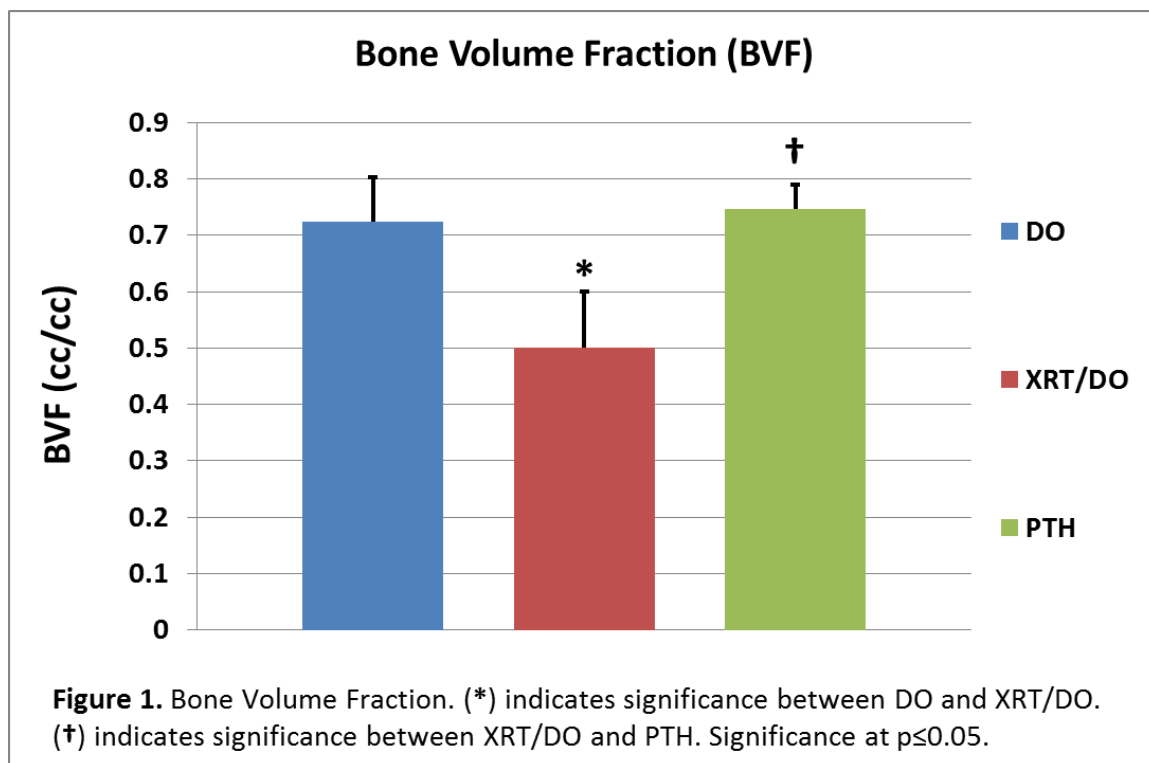
D Sarhaddi, BA; KK Gallagher, MD; SS Deshpande; CN Tchanque-Fossuo, MS, MD; A Donneys MS, MD; NS Nelson; H Sun, PhD; PH Krebsbach DDS, PhD; DB Chepeha, MD; SR Buchman, MD

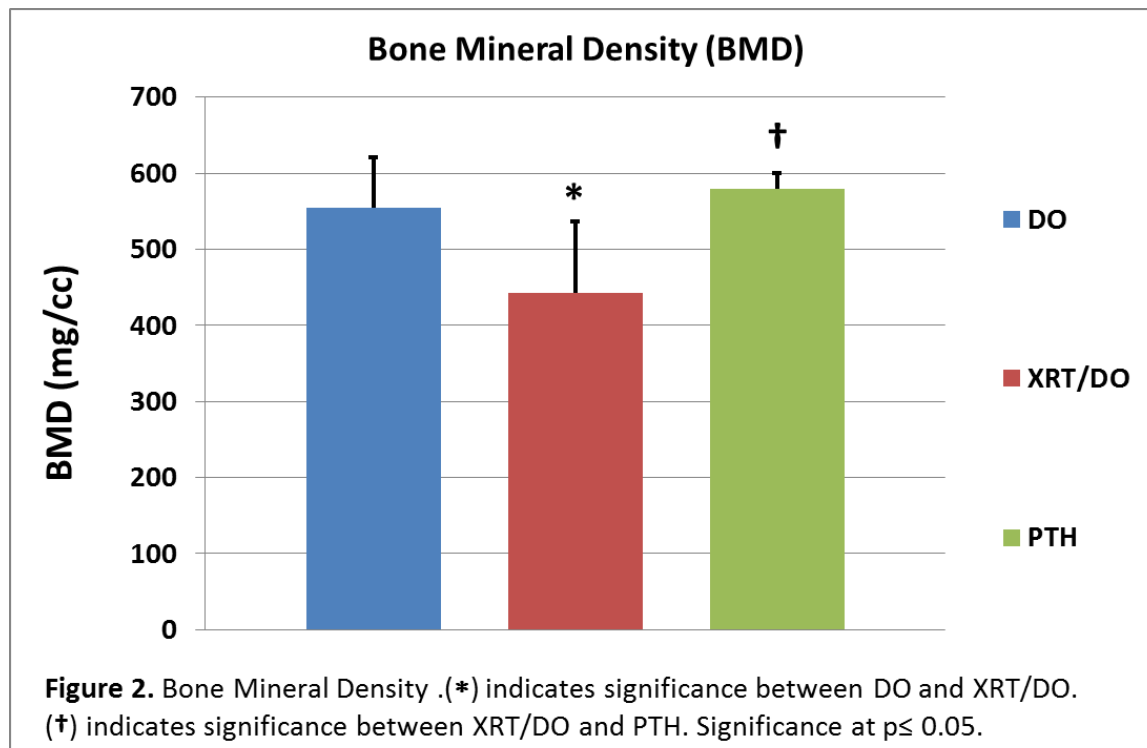
ABSTRACT

Background: The use of mandibular distraction osteogenesis for tissue replacement after oncologic resection or for defects caused by osteoradionecrosis has been described in limited clinical utility. Previous laboratory work has shown that radiation causes decreased union formation, decreased cellularity and decreased mineral density in an animal model of mandibular distraction osteogenesis. Our global hypothesis is that radiation induced bone damage is partly driven by the pathologic depletion of both the number and function of osteogenic cells. Parathyroid Hormone (PTH) is an FDA-approved anabolic hormonal therapy that has demonstrated efficacy for increasing bone mineral density for the treatment of osteoporosis. We posit that intermittent systemic administration of PTH will serve as a stimulant to cellular function which will act to reverse radiation induced damage and enhance bone regeneration in a murine mandibular model of DO.

Methods: 20 isogenic male Lewis rats were randomly assigned into 3 groups: group 1 (XRT-DO, n=7) and group 2 (XRT-DO-PTH, n=5) received a human bioequivalent dose of 70Gy fractionated over 5 days. All groups including group 3 (DO, n=8) underwent a left unilateral mandibular osteotomy with bilateral external fixator placement. Four days later, MDO was performed at a rate of 0.3 mm every 12 hours to reach a maximum gap of 5.1mm. Group 2 was injected PTH (60µg/kg) subcutaneously daily for 3 weeks following the start of MDO. On post-operative day 41, all left hemimandibles were harvested. µCT at 45 µm voxel size was performed and radiomorphometrics parameters of bone mineralization were generated. Union quality was evaluated on a 4 point qualitative grading scale. Radiomorphometric data was analyzed using one-way ANOVA and union quality assessment analyzed via the Mann-Whitney test. Statistical significance was considered at $p \leq 0.05$.

Results: Groups 1 and 2 appropriately demonstrated clinical signs of radiation induced-stress ranging from alopecia to mucositis. Union quality was statistically significantly higher in PTH-treated animals, compared to XRT-DO group animals ($p=0.02$). Mineralization metrics, including Bone Volume Fraction (BVF, Figure 1) and Bone Mineral Density (BMD, Figure 2) also showed statistically significant improvement. The groups that were treated with PTH showed no statistical differences in Union nor radiomorphometrics when compared to DO in non-radiated animals.





Conclusion: We have successfully demonstrated the therapeutic efficacy of PTH to stimulate and enhance bone regeneration in our irradiated murine mandibular model of DO. Our investigation effectively resulted in statistically significant increase in BMD, BVF, and clinical unions in PTH-treated mandibles. PTH demonstrates immense potential to treat clinical pathologies where remediation of bone regeneration is essential.

Disclosure: None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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