

Deferoxamine Enhances Bone Regeneration in Irradiated Mandibular Distraction Osteogenesis

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Background: Previous work in our lab demonstrated impairment of bone formation after irradiation (XRT), thus precluding the use of distraction osteogenesis (DO) as a reconstructive option for patients with head and neck cancer (HNC). One potential intervention to extend the DO procedure would be to augment the blood supply to the regenerate (RG). Deferoxamine (DFO) is an iron-chelator that has been shown to increase angiogenesis via the hypoxia inducible factor pathway. We posit that the angiogenic effect of DFO will function to improve bone regeneration in the mandible by augmenting the quality and quantity of bone. We used quantitative histomorphometry (QHM) to objectively measure the effectiveness of DFO to increase the osteocyte count and bone healing metrics in DO of the radiated murine mandible.

Methods: Two groups of Sprague-Dawley rats (n=15) underwent fractionated XRT of the left mandible, utilizing human equivalent doses for HNC. Both groups underwent placement of an external fixator, mandibular osteotomy, and 5.1 mm distraction over an 8 day period. During active distraction, the experimental DFO group (n=9) was treated with a 200uM DFO injection into the RG QOD. After 28 days of consolidation, mandibles were harvested decalcified, sectioned, and stained. Tissue-thresholding and point-counting of osteocytes and empty lacunae were performed within a region of interest using Bioquant software.

Results: We found a proliferation of osteocytes in the DFO treated RG when compared to the control group. DFO effected a significant increase in osteocytes per high-powered-field (46v43.6; $p<0.05$) as well as increase in bone volume fraction with subsequent decreased osteoid volume fraction. The QHM data also demonstrated a significant decrease in empty lacunae for the DFO group (3.2v11.4; $p<0.001$). The increase in cellularity with DFO in the RG could also be appreciated grossly within the region of the increased RG formation.

Conclusions: Our study demonstrates the effectiveness of DFO treatment to enhance the number of osteocytes within the RG in an irradiated murine mandibular DO model. Maintenance of full lacunae supports our findings of a positive cellular response to DFO therapy. Furthermore, tissue-thresholding confirms an increase in bone volume, more specifically, that of increased mineralized bone. The ability of improved cellularity to abrogate the devastating effects of XRT on bone formation may suggest utility for a broader range of clinical skeletal repair.