INTRODUCTION: Prolonged treatment time and disuse osteoporosis remain problematic in distraction osteogenesis (DO), with decreases of 44% - 61% in bone mineral density reported in adjacent bone. This study investigated the role of zoledronic acid (ZA), a new, potent bisphosphonate, in increasing bone formation and reducing osteoporosis in DO.

METHODS: Animal ethics approval was received (WAEC-177). Thirty 8-week-old New Zealand White rabbits had a 10.5 mm right tibial lengthening over 2 weeks (consolidation 4 weeks) with an M-100 fixator (Orthofix, Bussolengo, Italy). Rabbits were randomized to 3 groups - controls: saline only; ZA: 0.1 mg / kg at surgery as a 20 minute infusion; re-dosed ZA: additional infusion of 0.1 mg / kg at 2 weeks. Two rabbits were excluded due to premature consolidation identified to be fixator related.

Bone mineral content (BMC) and density (BMD) measurements were made in the AP projection at 2, 4 and 6 weeks with a LUNAR DPX densitometer (Norland, Ft Atkinson WI). Calibrated AP and lateral radiographs of the tibiae were taken after culling. Tibiae were analyzed with a Stratec XCT-960A pQCT scanner (Stratec, Pforzheim, Germany). 2 mm slices were obtained, 15 in the right (lengthened) tibiae and 10 in the left (non-operated) tibiae. Data were generated for BMD (g/cm3), BMC (g) and cross-sectional area (mm²). 4-point bend bending was carried out on an Intron machine at a displacement of 2 mm/min using a 10 kN load cell.

RESULTS: DEXA scans documented faster mineral accrual after distraction between 2 and 4 weeks in both treatment groups over saline controls (Fig. 1, ANOVA p<0.01).

| Non-Op | Left prox | 0.32 | 0.33 | 0.36*# |
|        | Left distal | 0.29 | 0.30 | 0.33*# |

Control ZA Redosed ZA

Qualitatively, the QCT images showed a delay in remodeling in the ZA treated specimens, with smaller intramedullary canals (Fig. 2).

There was a dose related reduction in the lengths of the non-operated tibiae of the rabbits, the mean values being 97.1 mm for controls, 92.3 mm for single dose and 89.8 mm for the re-dosed group (ANOVA p<0.01).

DISCUSSION: ZA therapy significantly increases new bone formation and reverses osteoporotic effects in rabbits undergoing DO. Remodelling is delayed, but delaying remodelling until the bone is returned to a physiological environment may be advantageous. Transient growth inhibition with bisphosphonate administration is of some concern, but this would be minimised in a one dose model, and is not relevant in adults.

Bisphosphonates have classically been thought to act as osteoclast inhibitors. There is increasing evidence that they have direct effects on osteoblasts also, including evidence that ZA can stimulate bone formation in osteoblast cell culture. Whether the large increase in regenerate formation seen with ZA administration results from direct osteoblastic effects or the reduction of osteoclast influence has not yet been determined.

ZA therapy has the potential to improve outcomes in distraction osteogenesis. Administration of ZA at or just after surgery would be a convenient and practical solution in the clinical setting. Clinical trials are needed to further evaluate this promising therapeutic strategy.

REFERENCES:
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48th Annual Meeting of the Orthopaedic Research Society
Paper No: 0039