INTRODUCTION: No reliable medical therapy has been developed for the prevention of collapse and deformity in patients suffering from osteonecrosis (ON). Based on our research showing increased bone formation in distraction osteogenesis, we hypothesized that Zoledronic Acid (ZA) could aid in the preservation of femoral head structure while simultaneously allowing revascularization and new bone formation.

METHODS: A model of traumatic ON was utilized in 24 female 14-week-old Wistar rats. Animal ethics approval was received (WAEC-197). The right femoral head was dislocated from the acetabulum, the ligamentum teres divided, and the entire femoral neck denuded of soft tissue by polishing with a vicryl suture. Rats were randomized in lots of 4 into three groups according to the schedule below. Zoledronic acid (Novartis) 0.1 mg/kg from commercial stock was administered by subcutaneous injection to treated animals, saline (S) to controls.

Animals were allowed rat pellet and water ad libitum and caged in groups of 4. Dual tetracycline labels were applied at weeks 4 and 5, and all animals were killed 6 weeks post-operation. One hour prior to culling 70 MBq Tc99 MDP was administered subcutaneously. Right and left proximal femora were harvested, fixed in 4% paraformaldehyde and faxitrone. Specimens were resin embedded for surgical treatment in early ON where architecture has not been met with mixed success. ZA therapy could potentially obviate the need for invasive treatment such as core decompression. Positive effects of bisphosphonates on osteoblasts are now widely known, as such ZA therapy may provide both anti-resorptive and pro-osteoblastic effects. Based on our hypotheses in designing this experiment on the knowledge that ZA administration leads to increased callus formation, mineralization and strength in distraction osteogenesis in rabbits were not consistent with these observations, as angiogenesis is a critical factor in bone formation. We based our hypotheses in designing this experiment on the knowledge that ZA therapy can lead to both anti-resorptive and pro-osteoblastic effects. Positive effects of bisphosphonates on osteoblasts are now widely known, they do not act on osteoclasts alone. As such ZA therapy may provide solutions for fractures prone to ON, such as in the femoral neck, talar neck or scaphoid, increasing new bone formation and preventing collapse from ON. ZA therapy may also be an extremely valuable adjunctive therapy when combined with surgery, possibly augmenting the effectiveness of minimally invasive treatment such as decompression. Zoledronic acid treatment prevented destruction of the epiphysis following osteonecrosis in this experiment over a six week period. Pre-treatment with ZA provided considerable protection from the avascular insult.

DISCUSSION: Administration of ZA reduced epiphyseal destruction (anti-resorptive effect) but also allowed new bone formation and mineralization (osteoblastic effect) leading to a viable, preserved epiphysis. The femoral necks were partially resorbed in the post treated group, we assume this occurred in the week prior to ZA administration, as this was not present to the same degree in the pre and post group. Further experiments designed to determine the timing of revascularization in ZA and control groups, as well as longer follow-up, are being undertaken. Osteonecrosis causes considerable disability in both the paediatric and adult population. Surgical options in the treatment of adult and childhood ON meet with mixed success. ZA therapy could potentially obviate the need for surgical treatment in early ON where architecture has not been completely destroyed. In children with Perthes disease, where the prognosis is directly related to femoral head sphericity, successful prevention of collapse is likely to provide superior outcomes to containment treatment. In many forms of ON, joint involvement is multiple and sequential. Treatment with ZA may prevent the destruction of other joints in these individuals. Other studies have suggested that ZA inhibits angiogenesis in the dose range used in this study, and as such, would not be expected to be a useful adjunct in the treatment of osteonecrosis. Our previous results showing that ZA administration leads to increased callus formation, mineralization and strength in distraction osteogenesis in rabbits were not consistent with these observations, as angiogenesis is a critical factor in bone formation. Bone scintigraphy scans showed a significant increase (P<0.01, ANOVA) in femoral head BMD and BMC for treated over control groups (Table II).

RESULTS: Representative radiographs are shown (Fig. 1). The femoral heads in the saline group were smaller as a percentage of the non-operated side, this effect was reduced (p<0.01, ANOVA) in the treated groups. Bone area, height and width of the femoral head were recorded and compared to the contralateral side. Scintigraphy scans were taken using 4mm aperture pinholes. BMD and BMC were measured with a pDEXA Sabre scanner (Norland, Ft Atkinson WI). Specimens were resin embedded and sectioned undecalcified. One control rat died and was not replaced.

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REFERENCES: