Efficacy of an injectable dual release delivery system for halting Perthes disease

Y. Zou,[1] J. Horstmann,[2] T.A. Milbrandt,[2,3] V. Talwalkar,[2,3] and D.A. Puleo[1]
[1] Center for Biomedical Engineering, [2] Department of Orthopaedic Surgery, University of Kentucky, Lexington, KY, USA
[3] Shriners Hospital for Children, Lexington, KY, USA

Statement of Purpose: Legg-Calvé-Perthes disease, also called avascular necrosis (AVN), is an idiopathic osteonecrosis of the immature capital femoral epiphysis that will lead to collapse of femoral head. The resulting joint distortion and incongruity can cause premature osteoarthritis leading to early total joint replacement surgery [AAOS and NONF, 1996; *J. Bone Joint Surg.* 66:860, 1984]. At present, there is no clinical treatment for halting progression of AVN [*Am Heart J.* 159:803, 2010]. Current treatments focus on containment and require either surgery and/or long recovery time.

To halt progression of femoral head collapse associated with Perthes disease, an injectable dual release drug delivery system was previously developed for localized, sequentially release of an anti-resorptive agent (clodronate) followed by an osteogenic agent (simvastatin). In of the present study, the efficacy of the delivery system for preserving the femoral head sphericity and internal architecture was evaluated in an established pig model of osteonecrosis.

Materials and Methods: AVN was induced unilaterally in the right leg of 12 3-week-old male piglets by ligation of the femoral neck. Nine animals received percutaneous intraosseous injection of the delivery system under fluoroscopy one week after surgery. The four experimental groups (three piglets each) were: untreated, vehicle (delivery system without drugs), clodronate only, and clodronate plus simvastatin (Clod+Sim). The left legs remained untouched and served as normal controls. Femoral heads were harvested from both sides six weeks after injection.

The external morphology (*e.g.*, height and sphericity) of the femoral heads was evaluated by gross observation of the explanted tissue. Overall bone structure was evaluated by radiography immediately prior to and following harvest.

The internal bony microarchitecture of the femoral heads was examined using microCT. Both qualitative assessment of structure as well as quantitative morphometry were conducted.

Results and Discussion: Both gross appearance (not shown) and X-ray analysis (Figure 1) showed that vehicle and Clod+Sim groups maintained similar sphericity compared to the normal control group. The height of Clod+Sim femoral heads was closest to that in the normal group. The untreated and clodronate groups suffered significant femoral head collapse and lost both height and sphericity.

With microCT, the internal bony microarchitecture of femoral heads was evaluated. The structure in the middle of representative bones from each group is shown in Figure 2. The Clod+Sim group had bone microarchitecture similar to that in the normal group, while the other three groups showed either collapse or defective microarchitecture. The bone volume (BV) and total volume (TV) of femoral heads were normalized to the normal control group to facilitate the comparison (Figure 3). The Clod+Sim group demonstrated values closest to the normal control group for both TV and BV, while the untreated and clodronate groups were the worst.

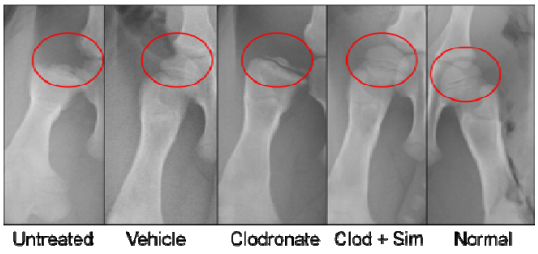

Figure 1. Radiographs of femoral heads before harvest.

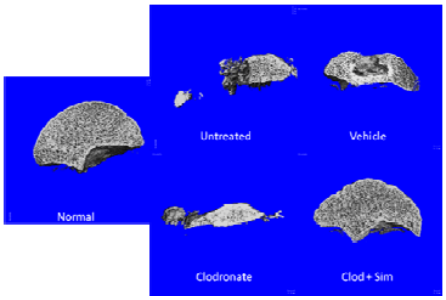

Figure 2. Bone microstructure at middle cut plane as visualized by microCT.

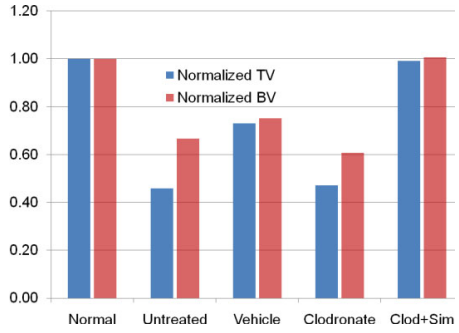

Figure 3. Bone volume (BV) and total volume (TV) measured by microCT.

Conclusions: This pilot animal study demonstrated the efficacy of an injectable dual release delivery system in halting the progression of AVN and preserving the sphericity of the femoral head. This progress can lead to a novel and practical treatment for AVN.

Acknowledgement: This work was supported in part by the University of Kentucky Department of Orthopaedic Surgery