Evaluation of an Absorbable Gentamicin Eluting Plate Sleeve in an Ovine Fracture Model

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Statement of Purpose: High-energy lower extremity fractures have been associated with surgical site infection (SSI) and osteomyelitis rates ranging from approximately 14% to 60% in both military and civilian settings [1]. Metal implants can serve as sites for bacterial adhesion and formation of a bacterial biofilm, increasing the risk of surgical site infections [2]. Locally delivered antibiotics hold promise for reducing SSIs, as they can be used to deliver high concentrations of antibiotics where needed and prevent the development of biofilms on the plate surface. Multiple studies in animals have demonstrated that if an implant surface can be protected from colonization by bacteria for a period of time immediately after surgery, the rate of SSI can be significantly reduced [3,4]. The recent development of an antibacterial plate sleeve (APS) allowing for controlled local delivery of gentamicin, has great promise in mitigating SSIs. The APS is a tubular thin film of absorbable polymer (Polyglytone® 6211) impregnated with gentamicin sulfate that fits over a fracture plate. The purpose of this study was to evaluate the effect of the gentamicin eluting APS on fracture healing in an ovine tibial osteotomy model using a single sleeve (1APS) or an exaggerated dose with 4 sleeves (4APS).

Methods: Forty-eight, skeletally mature, Dorset-cross ewes underwent a unilateral mid-diaphyseal tibial osteotomy, followed by open reduction internal fixation (ORIF) using a locking plate and bicortical locking head screws. The APS was fitted over the plate for the treatment cohorts (1APS or 4APS) while control cohorts (Cx) received no sleeve. Sheep were euthanized at 4 and 12 weeks postoperative. Outcome measures included: blood counts, serum chemistry, gentamicin plasma concentration, lameness scoring, and radiography for the in life phase. Explanted tibiae were analyzed using micro computed tomography (µCT), histopathology, and a semi-quantitative scoring to evaluate bone healing at the osteotomy site. Healing scoring utilized cranial, caudal, and lateral sections and the scores were subjected to principal components analysis.

Results:

Surgical procedures and general anesthesia were without complications and all animals had uneventful recoveries. One sheep sustained a catastrophic failure of the repair and was eliminated from the study. No abnormal findings were noted for clinical pathology, serum chemistry and gross necropsy observations in any of the study cohorts. Both treatment groups showed a peak plasma concentration of gentamicin at 1-4 hours, with detectable gentamicin plasma concentration out to 10 days (LLOD = 10 ng/ml). The highest concentration measured was a maximum plasma gentamicin concentration of 781 ng/ml. There were no significant differences in radiographic scores between 1APS, 4APS or Cx cohort at 12-weeks; there was a significant difference between 1APS, 4APS and Cx for the 4-week cohort ($P<0.05$). The statistical difference seen in the radiographs was related to callus morphology scores and was determined not to be clinically significant. There was no significant effect of treatment (1 APS, 4 APS) on lameness scores and all clinical observations were unremarkable. Macroscopic evaluation of the tibial osteotomy sites, including the soft tissue envelope, was unremarkable. µCT analysis corroborated normal bone healing and there were no statistical differences found among the three treatment groups (1 APS, 4 APS, or Cx) for bone volume (BV), BV/TV (total volume), and density in either the 4-week or the 12-week sheep. All osteotomy scores (bridging, fill, lamellar remodeling) at all sites (cranial, caudal, lateral) were significantly increased with time. For the principle components analysis, the osteotomy repair score factor was significantly affected by time, confirming the progression of healing from 4 to 12 weeks; it was also significantly lower in group 1APS than in group Cx at 12 weeks only, but was not significantly different between group 4APS and group Cx. In the absence of a dose-response the apparent effect in the 1APS group may represent variation in the fracture healing process rather than a biologically significant effect of treatment. Histopathology evaluation of the soft tissues surrounding the plate and screws showed no treatment dependent variations except for the presence of the polymer sleeve and an associated low grade chronic foreign body response. Polymer remnants of the APS implant were observed at 4-weeks postoperative but were not observed at 12-weeks, except in one animal (4APS).

Conclusions:

In summary, clinical observations, digital radiographs, µCT, histopathology, and bone healing assessments indicated that the APS technology applied to commercially available fracture hardware in this preclinical large animal model is safe. This study further demonstrated that a typical dose (1APS) and an exaggerated clinical dose (4APS) does not adversely impact the natural timeline of fracture healing when compared to empty controls. Future work aims to study 1) local gentamicin tissue concentrations and 2) the efficacy of the APS in a contaminated fracture healing model.

References: 1. Harris AM. J Orthop Trauma. 2009:23:1-6.)(2. Miclau T. J Orthop Trauma. 2010:24:583-6.)(3. Antoci V, Jr.. Clin Orthop Relat Res. 2007:461:88-95.)(4. Stewart S. JBJS Am. 2012 1;94(15):1406-15