Journal of Orthopaedic Translation (2016) 7, 116—118

Available online at www.sciencedirect.com

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journal homepage: http://ees.elsevier.com/jot

Session: Traumatology

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ESTABLISHMENT OF A COST-EFFECTIVE STEROID ASSOCIATED OSTEONECROSIS IN RATS

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Objective: We have successfully established steroid-associated osteonecrosis (SAON) animal model in rabbit with a single injection of lipopolysaccharide (LPS) and subsequently three injections of methylprednisolone (MPS). The present study tested an experimental protocol to induce SAON in rats as rat is more suitable animal model to study molecular mechanism of diseases and drugs as well as a cost-effective model to study body metabolism physiologically and pathologically.
Methods: Eight 24-week-old male Sprague-Dawley rats were induced SAON by pulsed injection of one intravenous injection of LPS (1mg/kg) and 24 hours later, three intraperitoneal injections of MPS (100 mg/kg) at a time interval of 24 hours. Animal Ethics Approval was obtained (Ref. No. 15-150-MIS). Additional 4 rats were used as normal controls. 2 weeks after induction, bilateral femora and bilateral tibiae were collected for histological examination. Diffused presence of empty lacunae or pyknotic nuclei of osteocytes in the trabeculae, with surrounding necrotic bone marrow were classified as osteonecrotic lesion. Rat with presence of at least one osteonecrotic lesion was considered as ON+ rat.
Results: Four rats died the following day after LPS injection with 50% mortality. The four remaining rats survived after the three injections of MPS and developed osteonecrosis based on histological evaluation with 100% incidence of SAON. Empty lacunae of osteocytes were found in the trabeculae. Edema and fibrous marrow appeared in necrotic bone marrow. In intact bone marrow region of the proximal femur, distal femur and proximal tibia, more newly formed small sized adipocytes were present in ON+ rat, while there were very few adipocytes in these regions in normal control rats. In distal tibia, there were full of large sized adipocytes in bone marrow in normal control rats, while the adipocytes were smaller and more mononuclear cells generated in bone marrow of distal tibia in ON+ rat, indicating activated repairing reaction in yellow bone marrow region in distal tibia of ON+ rat.
Conclusion: This study successfully induced SAON in rat model with pulsed injection of LPS and MPS, the pathological changes found in SAON patents and SAON rabbit model, e.g., empty lacunae in osteocytes, edema and fibrous marrow, were also found in our rat model. Further study will be on lower dose of LPS for its potential to decrease the mortality to facilitate translational study using innovative agents for prevention of SAON.
http://dx.doi.org/10.1016/j.jot.2016.06.136

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SCLEROSTIN ANTIBODY PROMOTES FEMORAL FRACTURE HEALING IN OVARIECTOMIZED RATS

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Introduction: Inhibition of sclerostin by systemic administration of a monoclonal antibody (Scl-Ab) significantly increased bone mass and strength at fractured bones in animal models and non-fractured bones in ovariectomized (OVX) rats. In this study, we examined the effects of Scl-Ab in a closed fracture healing model in OVX rats.
Methods: Sixty Sprague-Dawley rats underwent an ovariectomy or a sham operation at 4 months of age, and a closed fracture of the right femur was performed 3 months later. Subcutaneous injections with Scl-Ab (25 mg/kg) or saline were then administered on day 1 after the fracture and twice a week for 8 weeks (n=20 per group), at which time the fractured femurs were harvested for micro-computed tomography analysis, four-point bending mechanical testing and histomorphometric analysis to examine bone mass, bone strength and dynamic bone formation at the fracture site. The angiogenesis at the fracture site was also examined. Bone marrow stromal cells were also isolated from the fractured bone to perform a colony-forming unit (CFU) assay and an alkaline phosphatase-positive (ALP^+) CFU assay.
Results: OVX rats treated with Scl-Ab for 8 weeks had significantly increased bone mineral density and bone volume per trabecular volume compared with OVX rats treated with saline. Similarly, maximum load, energy to maximum load and stiffness in Scl-Ab-treated OVX rats were significantly higher than those in saline controls. The mineralizing surface per bone surface, bone formation rate per bone surface and mineral apposition rate were also significantly increased the Scl-Ab-treated group compared with the saline-treated group. Furthermore, the Scl-Ab-treated group had more CFUs and ALP^+ CFUs than the saline-treated group. No significant difference in angiogenesis at the fracture site was found between the groups.
Conclusion: Our study demonstrated that Scl-Ab helped to increase bone mass, bone strength and bone formation at the fracture site in a closed femoral fracture model in OVX rats. Bone marrow stromal cells in OVX rats injected with Scl-Ab also had increased CFUs and ALP^+ CFUs.
http://dx.doi.org/10.1016/j.jot.2016.06.137

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INTRODUCTION OF A NEW SURGICAL METHODOLOGY TO PERFORM EXPERIMENTAL CALVARIAL DEFECTS: PERFORMANCE OF CONVENTIONAL DENTAL STATION COMPARED TO ANSPACH DRILLING DEVICE IN A CADAVERIC STUDY

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Introduction: The calvarial defect model has been extensively studied and it is a popular choice for screening bone repair therapies. The current state of the art for creating such defects is to utilize a dental station (DS: trephine and burr). However, the risk of damaging the *dura mater* is high with this technique and subsequent animal exclusion cannot easily be minimized. In this study, we introduced a new system: the Anspach high-speed handheld drill (AD) to create standardized cranium osteotomies in cadaveric rabbit model. This drilling device has the great advantage to automatically stops the drill as soon as resistance to drilling is lost, making it a very safe method in regard to injury to underlying structures.
Subjects and Methods: Four craniotomies were performed on the skull of freshly euthanized female New Zealand White rabbits (n=33, of 35.8±3.5 wks weighing 3.9±0.38 kg), using either conventional dental station (DS, consisting of a trephine and burr, Fig. 1A) or the new Anspach drill (AD, from Depuy Synthes, Fig. 1B) and operation times were recorded. Exothermic reaction occurring during the drilling was monitored using a thermal camera. Following osteotomy, the integrity of the *dura mater* was scored and the skulls were harvested and scanned using tomography (ExtremeCT, Scanco) and the quality of the defects in terms of diameter and circularity was estimated using ImageJ analyses.