Magnetic Resonance-Guided Focused Ultrasound for Treatment of Arthritic Pain in a Sheep Model

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Introduction: Osteoarthritis (OA) is a significant problem worldwide and within the United States. One in five adults in the USA report having osteoarthritis with one in three people who are obese developing symptoms during their lifetime. Animal models provide clinically relevant ways to study effectiveness of the various treatments of osteoarthritis. Both rodent and non-rodent experimental models mimicking the lesions of OA have been developed using three different methods: spontaneous models, mechanical insult or surgically induced joint instability and extracellular matrix damage or interference in chondrocyte metabolism through substances such as mono-iodoacetate (MIA), collagenase, and steroids [1-2]. Smaller animals are useful because of their ease of use and cost, while larger animals are favorable because of their morphological comparability to humans. The anatomy of the sheep stifle is grossly similar to the knee joint of the human [1]. The OA models in sheep are nearly all surgically induced involving partial or total meniscectomy. Anterior (or cranial) cruciate ligament transection (ACLT) alone is reported to induce quite limited cartilage damage in sheep. Chemically induced OA models generally create an acute model for the study of acute cartilage degradation and joint pain. We found that there was no published report on MIA induced sheep OA models. Our goal was to observe morphological and histological changes using intra-articular injection of MIA to create OA model in the sheep and to test the safety and effectiveness of a novel method to treat OA pain - Magnetic resonance-guided focused ultrasound (MRgFUS) which is currently being widely investigated for numerous clinical applications [4].

Methods: Nine sheep (70 Kg average weight, 2 years old) were used for the project. In each of the sheep the right hind knee was injected with 0.7 g of sodium mono-iodoacetate on day 11 and day 31. The left knee was used to serve as a control. The sheep were observed for 12 weeks using a scoring system developed to measure the level of pain the sheep were experiencing using activity level, physical exam of the knee, and behavior. Additionally, to enumerate number of steps the sheep walked every day, three sheep were monitored using the pedometers. The sheep were also followed radiographically with imaging of the injected knee as well as the control knee. During weeks 7-9 the sheep were treated using MRgFUS directed at the interface of the knee chondral surface and the distal femur in order to target the nerves that supply the knee joint. The sheep were sacrificed and retrieved knee joints were fixed in 10% neutral-buffered formalin, decalcified in EDTA for 4 weeks. 6μm sections of the cartilage and sub-chondral bone of femoral condyles and tibial plateau of the knee joints were stained with Hematoxylin and Eosin (H&E) and Safranin-Orange-fast green (Safranin-O).

Results: All sheep developed osteoarthritis as revealed by radiographic and histologic examination (Fig.1). Cartilage lesions, associated with OA, were clearly seen. Large chondral erosions exposed the sub-chondral bone. No changes of typical degeneration were observed in the control knee joint of the sheep. Left knee joint articular cartilage was characterized by a smooth, polished and regular surface. Radiography indicated destruction of cartilage, which was confirmed by H&E and Safranin O staining. However, only 2 of the sheep, sheep 1 and 2 developed limping (pain indicator) after the development of arthritis. Both the sheep showed improvement in the pain scores following treatment with MRgFUS (Fig.2). Sheep 2 was monitored using a pedometer as well. The pedometer readings were in agreement with the pain scores of sheep 2. All other sheep showed no indication of limping and showed the pain score pattern as that of sheep 3. None of the sheep showed any signs of additional pain or limping following MRgFUS. Thermal dosing from the focused ultrasound did not show any histologic evidence of damage to nearby tissues after treatment (Fig.3).

Discussion: In this study, using morphologic and histological observations, we have characterized the typical pathologies of the disease induced in sheep knee joint by easy and rapid method of intraarticular injection of MIA. Sheep are quite useful as OA models since their knee joints are closer in size to humans compared to dogs and smaller animals. Thus, arthroscopy and MRI are feasible. We also demonstrated potential of MRgFUS for the treatment of osteoarthritic pain in the sheep model.

Significance: We were able to successfully develop a large animal model for osteoarthritis of the knee with all sheep demonstrating radiographic and histologic evidence of severe degenerative joint disease. The treatment of the sheep with MRgFUS was demonstrated to be safe with no evidence of damage to nearby tissues with the treatment. Further studies to reliably induce limping and to prove effectiveness of MRgFUS for the treatment of osteoarthritic knee pain are necessary using a larger number of sheep with a revised pain monitoring system for the accurate assessment.

References:
1. Di Paola, R, S Cuzzocrea. Predictivity and sensitivity of animal models of arthritis. Autoimmunity Reviews. 8; 2008: 73-75
2. Poole, R, S Blake, M Buschmann, S Goldring, S Laverty, S Lockwood, J Matyas, J McDougall, K Pritzker, K Rudolphi, W van den Berg, T Yaksh. Recommendations for the use of preclinical models in the study of treatment of osteoarthritis. Osteoarthritis and Cartilage. 18; 2010: S10-S16
3. Little CB, Smith MM, Cake MA, Read RA, Murphy MJ, Barry FP. The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in sheep and goats. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2010. 18 Suppl 3: S80-92.
4. Speed, CA. Therapeutic ultrasound in soft tissue lesions. Rheumatology. 2001; 40: 1331-1336