Intra-articular doxycycline-chondroitin sulfate application improves cartilage hardness in osteoarthritic rabbit knees

Ozlem Aydin1,2, Feza Korkusuz2,3, Petek Korkusuz3, Elif Bilgic3, Volkan Yaprakci4, Aysen Tezcaner5, Dilek Keskin2

1Ahi Evran University, Kirsehir, Turkey, 2Middle East Technical University, Ankara, Turkey, 3Hacettepe University, Ankara, Turkey, 4Afyon Kocatepe University, Afyon, Turkey

Background: Osteoarthritis (OA) is a non-inflammatory, degenerative joint disease, leading to pain, deformity and deterioration of function together with economic loss. Joint cartilage is avascular and systemic medicine may not efficiently reach/retained at the joint fluid. Doxycycline (D), a clinically used antibiotic with a matrix metalloproteinase activity, was combined with chondroitin sulfate (CS) to prevent the progression of OA. For this end, we designed doxycycline loaded and doxycycline-chondroitin sulfate co-loaded poly-ε-caprolactone (PCL) based drug delivery systems that can be applied to treat OA by intra-articular injection [1].

Aim: This study aims to provide a controlled local treatment approach by preventing the progression of OA and enhancing the regeneration of cartilage matrix with the use of two bioactive agents, D and CS. The efficacy of the system was investigated upon injection of the microspheres with hyaluronan (HA) into OA developed knee joints of rabbits.

Materials and Methods: Doxycycline loaded (DMS) and doxycycline-chondroitin sulfate co-loaded (D-CSMS) PCL (Mw of 14 kDa) microspheres were prepared using polyvinylalcohol (PVA- 4%) as emulsifier. Preparation details were described elsewhere [1]. Experimental OA was established by intra-articular collagenase type II (Clostridium histolyticum, Sigma) (4 mg/ml; 456 U/mg solid) injection into the hind knee joints of local albino adult male rabbits at day 1 and 4 [2]. Microspheres (DMS and D-CSMS), sterilized by gamma irradiation, were applied once by dispersing in 0.5 ml of hyaluronan (HA). After the establishment of OA, the treatment injections (HA, DMS and D-CSMS) were performed. Knees were followed for another 8 weeks and the joints were then harvested for radiological, histological and biomechanical evaluations.

Results: SEM image showed size and shape distribution of D-CSMS (Fig.1). Radiographic scores of both microsphere groups improved after 8 weeks of microsphere treatments compared to untreated OA joints. Histological scores had similar outcomes for both microsphere groups but also revealed the significance of combined use of D and CS; D-CSMS group significantly improved the Mankin/Pritzk er scores when compared with control group. Among treatments, D-CSMS group had the highest hardness value, which was significantly different than OA group, but not different than control group.

Conclusions and clinical implication: Both DMS and D-CSMS have potential for OA treatment via local controlled release system. However, D-CSMS had more pronounced positive contribution on all treatment outcomes and may be used on OA knee joints.

References:


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