Intra-articular Administration of a selective COX2-Inhibitor Suppresses Posttraumatic Joint Contracture in a Rabbit Model

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Introduction: Joint contracture due to trauma, surgery, arthritis or inflammatory conditions is detrimental to function. Rehabilitation and surgery may help improve range of motion, but residual or recurrent contractures are relatively common. Adjuvant pharmacological modalities could be of benefit in the prevention and treatment of joint contracture. The goal of this study was to determine the potential role of intra-articular Celecoxib administered via a hydrogel scaffold in joint fibrosis.

Methods: In vitro model: Human fibroblasts were exposed to selected concentrations of Celecoxib dissolved in DMSO (5, 10, 20 μM ). One hour prior to drug exposure, fibroblasts were stimulated with TGF-β, which differentiated them into myofibroblasts and activated extra-cellular matrix synthesis. After 24 hours of incubation, mRNA was extracted, and Col-1A and SMA expressions were measured by real-time PCR (n=4). XTT assay was performed to assess apoptosis and cell toxicity. Oligo(poly(ethylene glycol) fumarate) (OPF) hydrogels (N = 5) were loaded with Celecoxib, and drug elution properties were characterized by soaking the scaffolds in 1 ml of minimum essential media (MEM with 10 % fetal bovine serum). Each scaffold was transferred into a new Eppendorf tube with fresh media over a span of 14 days. The media drug concentration was evaluated via HPLC.

In vivo model: 24 skeletally mature New Zealand White (NZW) female rabbits were used utilizing a previously established model of joint contracture. A 3-mm defect was surgically created in the non-cartilaginous portions of the femoral condyle of the right knee, the joint was hyperextended to disrupt the posterior capsule and it was then immobilized in maximum flexion with a Kirschner-wire for 8 weeks. An OPF scaffold loaded with 1.8 mg Celecoxib in 10 μl DMSO (n=12) or an OPF scaffold with DMSO but without the drug (n=12, control group) was implanted intra-articularly. At 8 weeks, K-wires were removed, joint range of motion (ROM) was assessed radiographically, and rabbits were allowed free cage activity for an additional 16 weeks before sacrifice. After sacrifice limbs were mechanically tested using a custom-made joint ROM test system. Means of the two groups were compared using the two sample t-test with P-values of 0.05 or less being significant.

Results: In vitro: Celecoxib suppressed Col-1A and SMA expressions in a dose dependent manner. DMSO (control group) did not suppress TGF-β activation. XTT assay showed no toxicity up to 50 μM. Drug elution analysis revealed sustained delivery of Celecoxib at high doses ( 40μM) during a 14-day period. In vivo: After 8 weeks of immobilization, the Celecoxib group showed a statistically significant improvement in limb flexion contracture angle compared to the control group (62.3 degrees vs. 53.3 degrees, p<0.03). At 24 weeks the Celecoxib group showed additional suppression of joint contracture (121.1 degrees versus 99.5 degrees, p<0.01). No macroscopic joint damage was observed in either group.

Discussion: To date, no pharmacologic agent exists to prevent or alleviate arthrofibrosis. In this study, Celecoxib functions as an anti-fibrotic when delivered locally via implantation of an intra-articular hydrogel scaffold. Residual hydrogel was observed in several cases at the time of sacrifice, but no apparent inflammation or joint damage was observed. Further studies are forthcoming which will assess the safety of the OPF hydrogel. FDA-approved Celecoxib appears to be a promising and economic anti-fibrotic agent for suppressing post-traumatic arthrofibrosis evidenced by rabbit model data.

Significance: In-vivo and in-vitro results may be used for clinical trial in humans in the future.

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Source
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