Adjuvant rosiglitazone does not increase the effectiveness of surgical release in a model of arthrofibrosis

+1Barlow, J D; 1Hartzler, R U; 1Abdel, M P; 1Morrey, M E; 1Steinmann, S P; 1Sanchez-Sotelo, J; 1Morrey, BF
+1Mayo Clinic, Rochester, MN
Senior author: morrey.bernard@mayo.edu

ABSTRACT INTRODUCTION:

In order to better evaluate the formation and biology of these contractures, our group has developed a contracture model in the rabbit. This model has demonstrated formation of contracture over 8 weeks of immobilization following creation of cortical windows and hyperextension injury. Furthermore, this contracture has been shown to be quite stable, over as long as 16 weeks of remobilization. The contracture demonstrates biomechanical stiffness, as well as an increase in the number of myofibroblasts, a putative mechanism of contracture, in the capsule. By evaluating these parameters, a natural history of contracture is being developed.

This animal model facilitates testing of therapeutic procedures and agents in a controlled and reproducible setting. Unfortunately, it does not precisely mimic the timing of joint contracture formation. The model requires immobilization of the joint for eight weeks following injury. Clinically, contracture forms in spite of early passive range of motion. In addition, because the immobilization occurs over a period of eight weeks in the model, it is difficult to target potentially therapeutic interventions. For this reason, our group has developed a model in which a limited capsular release is completed in addition to the standard model. This allows an excellent window for therapeutic intervention.

Pharmacologic inhibitors of arthrofibrosis may reduce the formation of fibrosis in vivo. These agents have been investigated for the treatment of various other disease states, including scleroderma, and lung and renal fibrosis, but minimal work has been done to investigate their potential in joint contracture. TGF-beta has been a molecule that has been strongly implicated in the pathogenesis of fibrosis, both in joint contracture and other disease states. Efforts to modulate TGF-beta have been effective in decreasing fibrosis in these diseases. One class of agents that have been used as clinically safe modulators of TGF-beta are PPAR-gamma agonists. Multiple in vitro studies have demonstrated the ability of PPAR-gamma agonists to decrease fibrosis in vitro. In vivo effectiveness has also been clearly demonstrated in a scleroderma model, using rosiglitazone, a common medication for the treatment of diabetes.

METHODS:

Following IRB approval, twenty skeletally mature New Zealand White female rabbits were randomly divided into two study groups (Limited Capsular Release and Rosiglitzone groups). Rabbits in both groups underwent the same primary operation. Under appropriate anesthesia, they underwent lateral arthrotomy on the right knee. A 3 mm defect was created in the non cartilaginous portion of the femoral condyles. The joint was hyperextended to disrupt the posterior capsule. The joint was then immobilized in full flexion with Kirschner wires.

Animals in each group underwent a second operation 8 weeks after the primary operation. This second operation involved removal of the K-wire, manual lysis of bridging heterotopic ossification, and a limited contracture release (elevation of posterior capsule under tension). Animals in the rosiglitzone group were given 3 mg/kg of rosiglitzone in DMSO vehicle as a subcutaneous injection on the day of surgery and postoperative day one. Animals in the control group, as well as the limited capsular release group received placebo injections on the day of surgery and postoperative day one (DMSO vehicle alone). Beginning postoperative day two, animals in the rosiglitzone group were given 3 mg/kg oral rosiglitzone daily (in apple segments) until sacrifice. Animals in the control and limited capsular release group were given placebo daily (apple segments alone) until sacrifice. Compliance with the drug regimen and placebo were high, with no animals being excluded for lack of ingestion of the drug. All animals were closely monitored by veterinary staff. There were no side effects noted from the drug or placebo. No animal had to be withdrawn from the study secondary to drug administration or reaction.

All animals were mobilized for 16 weeks. Following 16 weeks of remobilization, all animals were sacrificed under anesthesia. The joints were immediately tested using a custom made testing device. This device was validated using standardized weights, and has been documented in the literature by our group. Briefly, the skin, muscle and tendons of the rabbit leg are dissected away, leaving tissue from the tibial tubercle up to approximately 10 mm proximal to the knee joint undisturbed. The tibia and femur are transected 7 cm from the joint line. The center of rotation of the joint is placed over the center of the torque cell. The position is confirmed fluoroscopically. This configuration is secured by intramedullary rods into the corresponding leg bones, which are attached to the torque arm. An extension torque is then applied through a pulley at 1 degree per second up to a maximum torque of 20 NCm. Flexion contracture was assessed by subtracting the angle at which the operative limb reached 20 NCm from the same parameter of the nonoperative limb.

Results are demonstrated as mean ± standard deviation. Statistical analysis was completed utilizing a Wilcoxon Rank Sum test. Significance was set at p<0.05.

RESULTS SECTION:

There were no intra-operative complications and no adverse reactions associated with rosiglitzone therapy. Surgical release was equally effective in improving joint extension in both groups (control, 29.5° ± 8.2°; rosiglitzone 34.3° ± 12.0°; p = 0.32). Following 16 weeks of remobilization, the difference in flexion contracture between the two groups was not statistically significant (control, 36.5° ± 14.2°; rosiglitzone 32.6° ± 10.6°; p = 0.39).

DISCUSSION:

In this model, there was no significant difference between the animals receiving oral rosiglitzone versus placebo. This is an unexpected finding given the current literature supporting the role of PPAR gamma agonists TGF Beta modulation and fibrosis. This may be related to low effective concentrations in the joint, or unknown systemic effects of the medication.

Further studies that quantified the concentration of the rosiglitzone in the joint, or deliver vehicles that provide high concentrations of rosiglitzone to the affected tissues may be a valuable next step in this line of research. This novel model, which includes a limited capsular release in addition to the previous model of arthrofibrosis, allows a convenient window for therapeutic intervention.

REFERENCES: