Intra-Articular Relaxin-2 as a Treatment for Arthrofibrosis

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Purpose: We propose the local intra-articular delivery of the naturally-occurring, antifibrotic hormone relaxin-2 as a novel treatment for arthrofibrosis. Relaxin-2 is endogenously upregulated during pregnancy to increase tissue laxity by promoting matrix metalloproteinase production, suppressing collagen and tissue inhibitors of metalloproteinases expression, and blocking transforming growth factor (TGF)-β1 signaling. Our proposal stems from clinical observation among arthrofibrosis-afflicted female patients who experienced lasting motion restoration and reduced joint pain during and after pregnancy. Given that articular structures are primarily responsible for long-term range of motion (ROM) loss in arthrofibrosis, we hypothesize that relaxin-2 will reduce fibrosis in a rat shoulder arthrofibrosis model.

Methods: 20 female Sprague-Dawley rats underwent surgical suture immobilization of the shoulder to induce fibrosis over the course of 56 days. After suture removal, recombinant human relaxin-2 was administered in 4 different treatment groups: (1) single intra-articular dose (sIA), (2) multiple intra-articular doses (mIA), (3) multiple intravenous doses (mIV), and (4) untreated operated surgical controls. Relaxin-2 was administered at a dose of 1.5 μg/kg in the sIA and mIA groups and at a dose of 0.5 mg/kg in the mIV group; mIA and mIV treatments were given every 2 days for 10 days. All kinetic measurements were recorded under anesthesia with a digitally controlled torque system, and normalized to each rat's baseline measurements.

Results: The total ROM of the untreated operated control group remained constricted by –24°, or –15% ($P < 0.01$) for the duration of the experiment when compared to unoperated baselines. Similarly, the mIV treatment group displayed a significant restriction of –31°, or –19% ($P < 0.01$). For the sIA group there was a temporary improvement in the total ROM measurement directly following the treatment ($P = 0.025$). However, the animals in the sIA group returned to a restrained total ROM by day 14 and remained restricted by –22°, or –14% ($P < 0.01$) for the duration of the experiment. The results from the mIA treatment group were significantly improved compared to the untreated control group ($P < 0.01$) and not significantly different from the healthy baseline measurements ($P = 0.94$).

Conclusion: In a validated rat shoulder contracture model, treatment with multiple intra-articular (mIA) injections of human relaxin-2 significantly improves total ROM, returning it to baseline levels collected prior to limb immobilization. A return to normal ROM is not observed with the sIA and mIV treatment groups. This suggests that a more sustained, lower level dosage is a more effective treatment. Arthrofibrosis is not restricted to the shoulder and is a widespread condition, occurring after trauma, surgical procedures, prolonged immobilization, and other etiologies. Local delivery of relaxin-2 offers a promising new treatment.