Anti-Inflammatory Treatment and Active Physical Therapy Have Differing Effects on Functional and Mechanical Properties in a Rat Model of Post-Traumatic Elbow Contracture

Rebecca F. Reals[1], Ryan M. Castile[2], Evan M. Bradley[3], Arun K. Movva[3], Alice Hu[2], Carson L. Hoopes[4], Aaron M. Chamberlain[5], Benjamin M. Zmistowski[6], Spencer P. Lake[1,2,6]

Departments of [1]Biomedical Engineering, [2]Mechanical Engineering and Materials Science, [3]Biology, and [6]Orthopaedic Surgery, Washington University in St. Louis, St. Louis, MO, [4]Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT, [5]Intermountain Health, Salt Lake City, UT

r.reals@wustl.edu

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INTRODUCTION: Traumatic elbow injuries such as fractures and dislocations result in post-traumatic joint contracture (PTJC) in up to 50% of patients [1], which can severely limit use of the upper extremity and adversely affect the ability to complete activities of daily living [2]. Physical therapy optimizes conditions to regain range of motion, but 12-15% of patients require more invasive treatments due to refractory stiffness [3]. Importantly, these treatment methods do not address the underlying biological mechanism of PTJC, which has been shown to involve inflammation [4, 5]. Cyclooxygenase-2 (COX-2), an enzyme that contributes to the inflammatory response through the conversion of arachidonic acid into prostaglandins, can be selectively inhibited by the drug celecoxib [6]. Studies in preclinical models of knee contracture showed that celecoxib treatment led to decreased joint adhesions and increased range of motion [7,8]. In our rat model of elbow PTJC, celecoxib administration decreased proportions of T cells and natural killer cells in the joint capsule [9]. However, it remains to be seen whether these changes in immune cell populations result in functional improvement of the affected limb. Furthermore, PTJC involves multiple tissues and cell types, and thus a multi-treatment approach will likely be needed to address all underlying causes. For example, biological modulation of the inflammatory response combined with physical disruption of fibrotic tissue may be more effective than either treatment alone. For this reason, we also explored the effects of anti-inflammatory treatment combined with physical therapy, specifically voluntary wheel running as it was shown to accelerate healing in other injury models (e.g., rat model of Achilles tendon rupture [10]). Therefore, the **objective** was to evaluate whether immunomodulation and physical therapy alone or in combination would alter the mechanical/functional properties of the injured elbow. We **hypothesized** that both celecoxib and wheel access would improve joint mechanics when administered alone compared to control, but combined treatment would exhibit greater improvement.

METHODS: *Injury Model:* In this IACUC-approved study, PTJC was induced in the left elbows of male Long-Evans rats (n = 8-10/group) through surgical transection of the lateral collateral ligament and puncture of the anterior capsule, followed by immobilization, according to a previously established protocol [11]. The injured elbow was immobilized with bandages for 21 days after surgery, then bandaging was removed to enable free joint mobilization for the subsequent 21 days. *Treatment Groups:* Following immobilization, animals received one of three treatments: physical therapy via continuous wheel access (WA) for voluntary running, daily doses of 50 mg/kg/day celecoxib administered orally via syringe feeding (CEL), or both wheel access and drug treatment (CELWA). Data from a group that received no additional treatment during remobilization (NT) and a group that was immobilized for the entire time period (42IM) were collected in a previous study and are included for comparison [12]. *Functional Testing:* During free mobilization, forelimb strength was measured weekly as previously described [13]. *Mechanical Testing:* After sacrifice, forelimbs were loaded in flexion-extension for five cycles; torque vs. angular position curves were analyzed to obtain total range of motion, maximum extension, maximum flexion, extension stiffness, and flexion stiffness (**Fig. 1.**). *Statistics:* One-way ANOVA with Dunnett's test was used to compare each treatment group to NT. Statistical significance was $p < 0.05$ where * indicates $p < 0.05$, ** indicates $p < 0.01$, and *** indicates $p < 0.001$.

RESULTS: Forelimb strength was decreased in CEL and CELWA groups compared to NT, while WA group was similar to NT **(Fig. 2.)**. Mechanical testing showed numerous differences between groups **(Fig. 3.)**. Compared to NT, max extension angle was significantly increased in the CELWA group and max flexion angle was significantly increased in the CEL group. Extension stiffness for all three treatment groups were significantly decreased; flexion stiffness was decreased in all three treatment groups but did not reach statistical significance. Total range of motion was significantly increased in CELWA.

DISCUSSION: This study showed that biological (celecoxib) and physical (wheel running) therapies had differing effects on functional and mechanical properties of the rat elbow in PTJC. Functional testing showed that CEL and CELWA injured limbs displayed lower forelimb strength compared to the NT, which may be attributed to muscle weakness caused by high doses of anti-inflammatory drug [14]. Delivering a lower dose of celecoxib or altering the initiation/duration of drug treatment may help attenuate inflammation without compromising muscle strength, thus highlighting the need to optimize the timing and dosage of a drug to maximize benefits while minimizing side effects. In the WA group, forelimb strength was approximately the same as the NT group. Post-mortem mechanical testing showed differing results depending on the parameter evaluated and on the treatment group. Compared to the NT group, maximum extension angle was significantly increased in the CELWA group while maximum flexion angle was significantly increased in CEL, indicating an improvement in extension but a worsening in flexion. However, previous work with our animal model showed max flexion is not significantly different from control while max extension is significantly impacted [11], so changes in extension mechanical testing parameters may have greater bearing on quality of life than flexion in human PTJC patients. Similarly, stiffness is known to be a debilitating consequence of elbow PTJC; when compared to the NT group, extension stiffness was significantly decreased in all three treatment groups. Flexion stiffness was also decreased in treatment groups compared to untreated animals but differences did not reach statistical significance. Taken together, results from our study show that voluntary physical therapy via wheel running, either alone or in combination with the anti-inflammatory drug celecoxib, warrants further investigation as a potential treatment for elbow PTJC.

SIGNIFICANCE/CLINICAL RELEVANCE: Current treatments for elbow PTJC are often ineffective in restoring full range of motion in the affected limb, thus there is a need for improved treatments. Here, we showed that the administration of voluntary physical therapy, the anti-inflammatory drug celecoxib, or both in combination altered functional forelimb strength and post-mortem mechanics of injured elbows**.** Future work will evaluate whether anti-inflammatory drug treatments and voluntary physical therapy will result in functional improvements in gait parameters or alter composition/organization of joint tissues.

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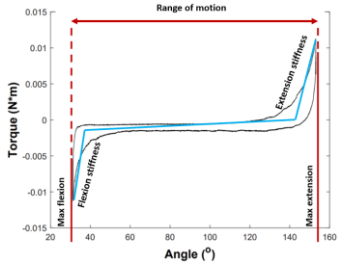

Fig. 1. A representative torque-angle loading curve from mechanical testing.

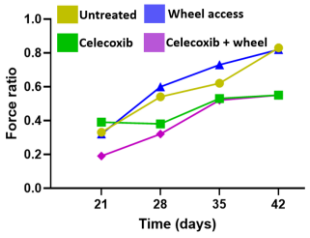

Fig. 2. Forelimb strength ratio in injured vs. contralateral arms, presented as mean of each group.

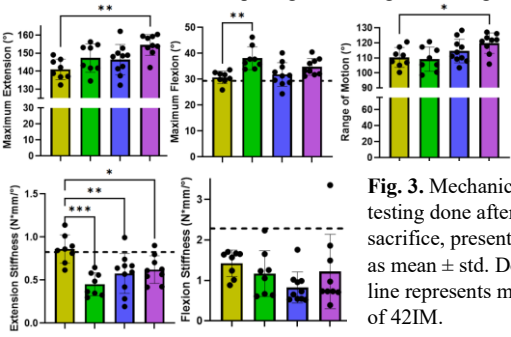

Fig. 3. Mechanical testing done after sacrifice, presented as mean ± std. Dotted line represents mean of 42IM.