THE EFFECTS OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS ON LIGAMENT HEALING: A MECHANICAL AND BIOCHEMICAL ASSESSMENT

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Introduction: Ligament injuries are among the most frequently sustained injuries in both the work place and in the sporting arena. The initial treatment of these soft tissue injuries has evolved to include a regimen of activity modification, ice, compression, elevation and nonsteroidal anti-inflammatory drugs (NSAIDs). Despite the frequent use of these medications, their impact on the healing of injured ligaments has yet to be established. Previous efforts to determine the effects that NSAIDs have on healing ligaments have focused on ultimate failure strength as the primary outcome measure, with varied results. [1] [2] [3] [4] [5] The material property of ultimate failure stress has never been reported in healing ligaments treated with NSAIDs. There is evidence to suggest that ligaments and tendons function in normal daily activity under repeated or sustained low loads. [6] [7] [8] It may therefore be more applicable to the in vivo situation if creep were measured in addition to ultimate failure strength and ultimate failure stress. The objective of this work was to determine, using ultimate failure load and the previously unreported measures of failure stress and cyclic creep, what effects systemic administration of NSAIDs has on early and intermediate ligament healing intervals.

Methods: With prior approval from the Animal Care Committee at the University of Calgary, 78 female New Zealand white rabbits underwent a surgical bilateral medial collateral ligament (MCL) transection. The rabbits where then divided into 4 treatment groups. Rabbits were dosed for the duration of the project with either oral Ibuprofen 18mg/kg BID (group I), a COX-2 inhibitor (DFP) 3mg/kg daily (group D), a placebo sugar solution (group P), or no treatment (group N). Animals were housed one per cage and allowed unrestricted activity. MCLs were tested after 3, 6, and 14 weeks of healing. High load mechanical outcomes investigated were ultimate failure strength, ultimate failure stress, and stiffness. Low load cyclic creep testing was performed from 0.1N to 15N at 1 Hz for 1 hour (3600 cycles). Results were analyzed using a one-way ANOVA with Bonferonni correction ($p<0.05$). Cross-sectional area measurements and water contents of the ligaments were also recorded.

Results: At 3 weeks of healing NSAID treatment resulted in a significantly greater failure load ($I3 = 67.3 \pm 26.8$ N) as compared to placebo ($P3 = 37.9 \pm 10.8$ N) ($p<0.01$). (Figure 1) Failure stress was greater than placebo, 4.63 ± 1.8 MPa and 2.83 ± 1.8 MPa respectively ($p<0.025$); as was cross-sectional area, $12.1 mm^2 \pm 2.9$ and 8.9 ± 4.3 mm^2 respectively ($p<0.05$). The untreated group had a comparable mean failure load ($N3 = 64.0 \pm 38.4$ N) to the NSAID groups.

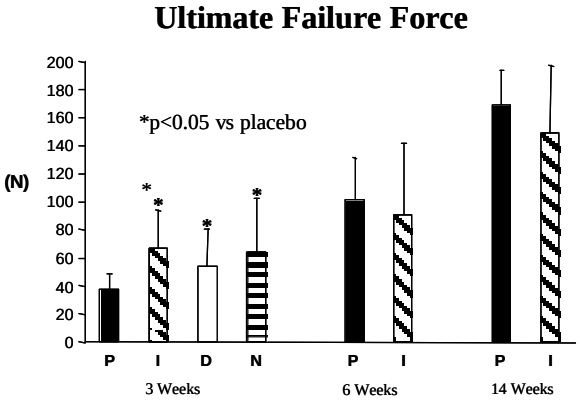


Figure 1: Ultimate failure force at 3, 6, and 14 weeks of healing.

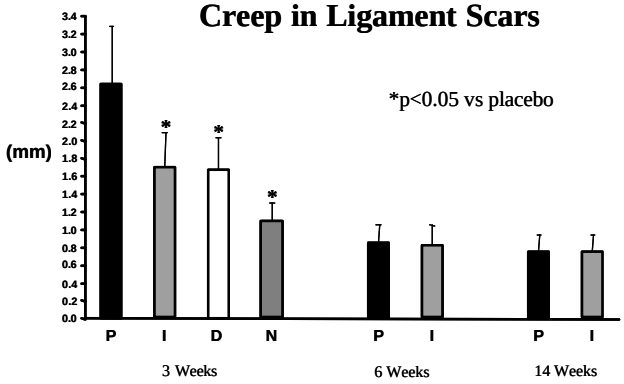


Figure 2: Creep in ligament scars at 3, 6, and 14 weeks of healing

The viscoelastic property of total creep was less in the NSAID treated group (1.71 ± 0.4 mm vs. 2.64 ± 0.7 mm for placebo) ($p<0.025$) at 3 weeks of healing (Figure 2). The untreated group also had less total creep ($N3 = 1.10 \pm 0.20$ mm) than the placebo group at 3 weeks. At 6 and 14 weeks these differences were no longer present. There were no significant differences in the water content of the ligaments from any treatment groups.

Discussion: Using previously unreported properties in NSAID treated ligament injuries, we have shown that NSAIDs improve both the high load and low load mechanical properties of injured ligaments in the early healing period compared to placebo treated injuries. When compared to placebo treatment, the material property of failure stress is greater in the NSAID treated ligament scar, indicating a superior scar quality. As well, the cross sectional area of this group was greater than placebo at 3 weeks of healing, indicating a more abundant scar formation. The finding that the ligaments from the untreated animals had superior high and low load properties was unexpected and further investigation in this regard is currently being undertaken.

These results demonstrate that NSAID treatment following ligament injury produces ligaments with similar high and low load properties as untreated ligaments. This work suggests that NSAIDs have no inhibitory effects on ligament healing. As NSAIDs are effective analgesics and will provide patients with pain relief following injury, this data supports their use as part of the treatment regimen following acute ligament injury.

References: (1) Dahners et al, Am J Sports Med, 1998. (2) Elder et al, Am J Sports Med, 2001. (3) Moorman et al, Am J Sports Med, 1999. (4) Vogel et al, Connective Tissue Research, 1977. (5) Almekinders L et al, Sports Medicine, 1990. (6) Holden et al, Biomechanics, 1994. (7) Butler et al, Abstracts of the Third World Congress of Biomechanics, 1998. (8) Yamamoto et al, Abstracts of the Third World Congress of Biomechanics, 1998.

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