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The Effect of Corticosteroids on Activated Human Synoviocytes: Implications for Intra-Articular Therapy

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Summary:
Steroid-treated synoviocytes significantly increase production of tissue inhibitors of metalloproteinases (TIMPs), which may serve to antagonize destructive mediators in the joint environment

Abstract:
INTRODUCTION
While the effect of corticosteroids on cartilage and chondrocytes has been studied in cell and tissue culture, considerably less attention has been given to the effect of corticosteroids on the synovium. Fibroblast-like synoviocytes (FLS) compose 80% of the normal human synovium and produce a variety of signaling molecules, including pro-inflammatory cytokines and matrix metalloproteinases (MMPs) that can mediate cartilage catabolism. Increased local inflammation in the setting of OA is largely attributed to FLS activation. Intra-articular injection agents including corticosteroids, local anesthetics, and biologics such as platelet-rich plasma (PRP) interact with all intra-articular structures, including synoviocytes. The purpose of this study was to determine the effect of corticosteroids on both cell viability and inflammatory mediator production of activated synoviocytes.

METHODS
Type B human FLS were activated via incubation with IL-1B for 24 hours and treated with Dexamethasone sodium phosphate, Methylprednisolone acetate (Depo-Medrol®), Betamethasone sodium phosphate and Betamethasone acetate, or Triamcinolone acetonide for the average duration of drug action (7, 9, 14 days, respectively). Each steroid-treated group was compared with its appropriate, time-matched control. Cytokine production was analyzed and statistical analysis was performed using one way ANOVA with $p<0.05$.

RESULTS
Pro-Inflammatory Mediators: In the triamcinolone acetonide group, the concentration of VEGF was significantly greater in controls (163 vs. 97, $p=0.025$). Similarly, VEGF concentration was greatest in control groups versus both methylprednisolone acetate and dexamethasone sodium phosphate groups (140 vs. 87 vs. 56, $p=0.029$) as was the concentration of MMP-1 (247 vs. 31 vs. 38, respectively, $p<0.001$). For methylprednisolone acetate and dexamethasone sodium phosphate, IL-6 was greatest in control synoviocytes versus both steroid-treated groups (2052 vs. 551 vs. 404, $p=0.011$). There were no significant differences in TNF-a, IL-1B, IFN-gamma, or MMPs-3, 9, 13 between the controls and any of the corticosteroid-treated groups (p-values > 0.05).

Anti-Inflammatory Mediators: The concentration of TIMP4 was significantly greater in triamcinolone acetonide-treated synoviocytes versus controls (104 vs. 1046, $p=0.014$) and in cultures treated with Betamethasone sodium phosphate versus control cultures (338 vs. 117, $p=0.013$). TIMP4 concentration was also greatest in synoviocytes treated with dexamethasone sodium phosphate compared with both methylprednisolone treatment and control cultures (302 vs. 160 vs. 78, $p=0.019$). TIMP1 concentration was greatest in synoviocytes treated with dexamethasone sodium phosphate, followed by control cultures, and finally cultures treated with methylprednisolone acetate (59574 vs. 50831 vs. 16890, $p=0.05$). There were no significant differences in IL-1ra or IL-10 production between any of the individual steroids and their corresponding control groups ($p>0.05$).

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CONCLUSION

Synoviocytes treated with IL-1ß alone demonstrated a significant increase in pro-inflammatory mediators including MMP-1, IL-6, and VEGF. These mediators have been widely implicated in the pathogenesis of osteoarthritis. IL-1ß-activated synoviocytes subsequently treated with corticosteroids show decreased levels of IL-6 and MMP-1 pro-inflammatory mediators. Steroid-treated synoviocytes significantly increase production of tissue inhibitors of metalloproteinases (TIMPs), which may serve to antagonize destructive mediators in the joint environment.