Dexamethasone Inhibits Inflammation and Cartilage Damage in a New Model of Post-Traumatic Osteoarthritis

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ABSTRACT: Corticosteroids are used in musculoskeletal diseases, and offer patient relief. Injections of corticosteroids are recommended for management of osteoarthritis (OA). Current data have shown the role of corticosteroids in ameliorating pain. We hypothesized that repeated intra-articular injections of high dose dexamethasone would protect the cartilage from damage in a post-traumatic model of OA. Eighteen female New Zealand White rabbits were used. Twelve underwent surgery to induce OA; six of them received intra-articular injections of dexamethasone every 3 days for 3 weeks. The other six rabbits served as operated controls. Six additional rabbits served as non-operated controls. All animals were euthanized 3 weeks post-surgery. Knees were assessed grossly. Cartilage, synovium, and fat pad were assessed histologically. Synovium and fat pad were analyzed with qPCR and Western blots. Surgical controls had cartilage damage which was suppressed with dexamethasone. Dexamethasone significantly decreased synovial expression of interleukin-1β and collagen I, and a trend to decrease synovial matrix metalloproteinase3 expression. There were also significantly lower levels of interleukin-1β protein with dexamethasone treatment. Dexamethasone significantly decreased fat pad expression of matrix metalloproteinase13, basic fibroblast growth factor, and interleukin8, and a trend to decrease matrix metalloproteinase3 and transforming growth factorβ expression. Dexamethasone decreased joint inflammation and joint tissue degradation and was chondroprotective in this unique model of PTOA. © 2013 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 32:566–572, 2014.

Keywords: knee; dexamethasone; cartilage; corticosteroids; OA

Osteoarthritis (OA) is one of the leading causes of disability worldwide, affecting over 4.5 million Canadians. OA commonly occurs after joint injuries. Anterior cruciate ligament (ACL) injuries and other knee injuries are the most common cause of secondary OA. While there have been many surgical advances in the treatment of knee injuries, there seems to be little improvement in the natural progression of OA. This has stimulated a debate amongst researchers regarding the mechanisms driving OA; resulting in a theory that inflammation is important in the pathogenesis of OA.

Numerous studies have investigated the efficacy of intra-articular injections of corticosteroids in the management of OA symptoms. In a review Ringdahl and Pandit found that corticosteroid injections reduced pain in the short-term compared to placebo; however, there was no evidence of long-term benefits. These studies also showed no adverse effects with short-term corticosteroid use.

Dexamethasone is a potent corticosteroid that has a high binding affinity to intracellular glucocorticoid receptors enhancing transcription of anti-inflammatory cytokines such as interleukin 1 receptor antagonist (IL-1Ra) and interleukin 10 (IL-10), and repressing transcription of pro-inflammatory cytokines, such as interleukin 1β (IL-1β), interleukin 6 (IL-6), cyclooxygenase 2 (COX2), and tumor necrosis factor α (TNFα).

Dexamethasone also has an effect on cartilage potentiating chondrocyte differentiation and proteoglycan synthesis in vitro, and reduced glycosaminoglycan loss in cartilage injury in vitro. Dexamethasone enhances progenitor cells to differentiate into chondrogenic cells and synthesize proteoglycans.

As dexamethasone is a potent anti-inflammatory and it is potentially chondroprotective in vivo, we sought to investigate its role in inhibiting inflammation and cartilage damage in a model of post-traumatic OA (PTOA). We hypothesized that frequent high dose intra-articular injections of dexamethasone would decrease inflammation post-injury and prevent cartilage changes in a “non-mechanical” model of PTOA.

MATERIALS AND METHODS

Animal Model

Eighteen mature female New Zealand White rabbits were used to investigate the role of dexamethasone as described by Huebner et al. Twelve rabbits underwent drill hole bone-injury surgery to induce PTOA; six of them received intra-articular dexamethasone injections (called DEX) and the other six rabbits served as operated, surgical controls. The remaining six rabbits served as non-operated, untreated controls. All animal work was approved (M08085).

PTOA Surgery

Twelve rabbits underwent surgery of the right hind limb to induce bone injury using intra-articular drilling. Animals returned to normal cage activity immediately after surgery and were euthanized 3 weeks post-surgery.

Dexamethasone Injections

Six of the twelve PTOA surgery animals were randomly allocated to the dexamethasone treated group (DEX). Dexamethasone is a potent corticosteroid that has a high binding affinity to intracellular glucocorticoid receptors enhancing transcription of anti-inflammatory cytokines such as interleukin 1 receptor antagonist (IL-1Ra) and interleukin 10 (IL-10), and repressing transcription of pro-inflammatory cytokines, such as interleukin 1β (IL-1β), interleukin 6 (IL-6), cyclooxygenase 2 (COX2), and tumor necrosis factor α (TNFα). Dexamethasone also has an effect on cartilage potentiating chondrocyte differentiation and proteoglycan synthesis in vitro, and reduced glycosaminoglycan loss in cartilage injury in vitro. Dexamethasone enhances progenitor cells to differentiate into chondrogenic cells and synthesize proteoglycans.
methasone (Dexamethasone 5, Vetoquinol N.A. Inc. Laval-
trie, QC) was injected intra-articular in the right knee joint at
a dose of 0.5 mg/kg. This dose was chosen based on previous
studies in rabbits and rats10,11 in order to fully inhibit
inflammation. The initial dose was given at surgery, a second
dose was given 6 h post-operatively, then injections were given
every third day until the time of euthanasia at 3 weeks.

Gross morphology of the joint was assessed qualitatively
for osteophytes, cartilage lesions, discoloration, and fibrilla-
tion by two experienced observers. Fat pad, articular car-
tilage, and synovium from the femoral groove and
suprapatellar region were collected. Cartilage samples were
taken from: femoral groove, patella, lateral and medial
femoral condyle, and lateral and medial tibial plateau.

**Histology**

**Cartilage**
Cartilage was embedded in Tissue-Tek® O.C.T.TM (Sakura
Finetek USA, Inc., Torrance, CA), flash frozen in isopentane
on dry ice, and cryosectioned (5 μm). Slides were stained
with Safranin-O/Fast-green and graded blind by one observer
twice with a modified Mankin score.6 Six sections from each
area of each joint were analyzed. As no differences were
found across different areas of the joint, they were summed.

**Synovium**
The synovium was embedded and cryosectioned (10 μm).
Slides were stained with Hematoxylin and Eosin. Synovial
membrane thickness was analyzed with Image J software
(National Institute of Health, Bethesda, MD) taking an
average thickness of three sections for each animal.

**Immunohistochemistry of Fat Pad**
The fat pad was embedded and cryosectioned (10 μm).
Slides were probed with one of six primary antibodies: IL-8 (1:1,500
mouse monoclonal; Abcam Inc.), IL-1Ra (1:750 mouse monoclonal;
Abcam Inc.), bFGF (1:2,000 goat polyclonal; Santa Cruz), TGF
(1:2,000 mouse monoclonal; Abcam Inc.), IL-1β (1:2,000 goat polyclonal;
Santa Cruz), and macrophage marker MAC387 (1:1,000
mouse monoclonal; Abcam Inc.), and then stained with one of
two HRP-conjugated secondary antibodies: Goat anti-mouse
HRP (1:200; Novus Bio, Oakville, ON), and Donkey anti-goat
HRP (1:250; Novus Bio). All slides were then stained with
diaminobenzidine (SigmaFast DAB with Metal Enhancer;
Sigma–Aldrich Co., St. Louis, MO) and analyzed with
Axiofire 2 (Carl Zeiss, Thornwood NY). The sections were
scored blind on a scale of 0 to 3 based on the level of stain.

**Real-Time Reverse Transcriptase Polymerase Chain Reactions**
(qPCR)
The synovium and fat pad of non-operated controls, surgical
controls and DEX animals’s right hind limbs were examined for
expression of inflammatory markers: IL-1β, IL-8, IL-6, and TNFα,
and for degradative markers: matrix metalloproteinases MMP3 and
MMP13, for growth factor markers critical in cartilage
maintenance: transforming growth factor β (TGFβ), and
fibroblast growth factor (bFGF), and for the connective tissue
marker collagen I. All samples were normalized to 18S
mRNA. Expressions were analyzed using qPCR as described
by Reno et al.12 See Table 1 for primer sequences.

**Western Blots**
The fat pad and synovium of non-operated controls, surgical
controls and DEX animals’s right hind limbs were examined for
protein levels (n = 4). Protein extraction, loading, and
separation were done as previously described by Huebner
et al.13 Membranes were incubated with antibodies directed
against bFGF (1:750; Santa Cruz) or IL-1Ra (1:750; Santa
Cruz) or IL-1β (1:1000; Santa Cruz) or IL-6 (1:750; Santa
Cruz) or IL-8 (1:1000; Abcam) or TGFβ (1:1000; Abcam) at
4°C overnight. Membranes were incubated for 1 h at room

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**Table 1.** Primer Sequences Used for qPCR Analysis

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<td>X 03205</td>
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temperature in an HRP-conjugated secondary antibody: bFGF, IL-1Ra, IL-1β, and IL-6 were incubated with anti-goat IgG (1:5,000; Novus Biotechnology). GAPDH, TGF-β1 and IL-8 were incubated with anti-mouse IgG (1:5000; Novus Biotechnology). The membranes were developed and quantified by densitometry. Antibodies directed against GAPDH (1:2,000; Abcam) were used as a loading control.

**Statistical Analysis**

Statistical analysis of cartilage Mankin scores was performed with ANCOVA with Bonferroni post-hoc (CI = 95%). Scores were also compared between joint locations and subscores with ANCOVA with Bonferroni post-hoc (CI = 95%). Synovial membrane thickness was analyzed with a UNIANOVA with LSD post-hoc (CI = 95%). Immunohistochemistry data were analyzed with a MANOVA with LSD post-hoc. All qPCR and Western blot data were analyzed using a MANOVA with Bonferroni post-hoc and confirmed with a Kruskal–Wallis test with Tukey HSD post-hock. All tests used unequal variance assumptions and non-parametric statistics were performed to confirm results to account for size differences between groups and variability within groups. A p < 0.05 was considered significant (SPSS; IBM, Armonk, NY).

**RESULTS**

During the course of the study non-operated and surgical controls appeared healthy, were active in their cages and maintained a normal diet and fluid intake. All animals including DEX animals regained baseline activity moving around their cages within 6 h of surgery (not quantified) and they continued to be mobile over the 3-week course of this study. DEX animals ate and drank more than other animals (not quantified) and lost weight despite increasing their caloric intake. DEX animals lost an average of 11.25% body weight (range 2–28.89%), while the other groups had no gain or loss of weight. In addition to weight loss, changes were noted upon gross inspection of the organs of the DEX animals during necropsy. The DEX hearts were relatively fibrous with heterogeneous pigment changes, the lungs appeared more edematous with fibrotic and necrotic areas, the livers had some areas of necrosis and were friable, and the kidneys were yellowed, nephrotic tissue was heterogeneous in appearance, and their internal architecture was distorted.

**Cartilage and Synovium—Gross and histology**

Signs of gross surface damage were apparent in the surgical control animals, showing some fibrillation and discoloration. The DEX animals had no signs of cartilage damage; their articular cartilage was indistinguishable from non-operated controls.

The gross findings were consistent with the microscopic changes seen with histology. Surgical control animals had abnormal cartilage with chondrocyte cloning, surface damage, and loss of safranin-O staining. Non-operated controls’ right and left cartilage had significantly lower Mankin scores than operated controls left knees (p = 0.036) and right knees (p < 0.0001). Non-operated controls’ Mankin scores did not differ from DEX animal scores (p > 0.05). Operated control’s left limbs had significantly higher Mankin scores compared to DEX right (p = 0.034) and left (p = 0.013) limb scores. Their right limbs also had significantly higher Mankin scores compared to DEX right (p < 0.001) and left (p < 0.0001) limb scores (Fig. 1). Operated controls right limb had significantly higher Mankin scores than their non-surgical left limb (p < 0.0001). There were no differences between right and left limbs within non-operated control and DEX groups (p > 0.05). There were no differences between subscores nor joint locations (p > 0.05), therefore the Mankin scores above were pooled and averaged for a total joint score for each animal.

The synovium did not differ in thickness among the operated groups (p > 0.05), and there was no difference in cell infiltrate present (p > 0.05).

**Immunohistochemistry**

TGF-β1, bFGF and IL-1Ra were not significantly different in level of positive stain between groups (p > 0.05). The right fat pad of surgical control had significantly more positive stain for IL-8 (p = 0.004), IL-1β (p = 0.002), and MAC387 (p = 0.005) than non-operated controls. Although not statistically significant, DEX samples had lower levels than surgical controls. These makers did not differ between DEX and control groups (p > 0.05).

**qPCR**

mRNA expression of synovial IL-1β was significantly greater in the right limb of surgical controls than the right limb of DEX animals (p = 0.015) (Fig. 2a). Collagen I expression was also significantly higher in surgical control synovium compared to DEX synovium (p = 0.002) (Fig. 2b). mRNA expression of synovial MMP3, although not statistically significant, was lower in DEX compared with surgical controls (p > 0.05; Fig. 2c). There were no other differences in mRNA levels in the synovium between groups.
In the fat pad, the surgical controls had higher expression of MMP13 and bFGF compared to non-operated controls \( (p = 0.014 \text{ and } p = 0.01, \text{ respectively}) \) and DEX \( (p = 0.012 \text{ and } p = 0.006, \text{ respectively}) \) (Fig. 3a and b). Unexpectedly, the DEX right limb fat pad IL-8 expression was significantly higher than non-operated controls \( (p = 0.006) \), surgical controls \( (p = 0.006) \), and DEX left limb \( (p = 0.007) \) (Fig. 3c). While not significant, DEX had lower mean expression of MMP3 and TGF\( \beta \) compared to surgical controls. There were no other differences in mRNA levels in the fat pad between groups.

**Western Blots**

bFGF protein levels in the synovium were lower after dexamethasone treatment than 3 week surgical controls \( (\text{NSD } p > 0.05) \). There were significantly lower protein levels of IL-1\( \beta \) in the synovium from the right leg in DEX compared to surgical controls \( (p = 0.027) \). However, there were no differences in the levels of IL-6, IL-8, or TGF\( \beta \) protein with dexamethasone treatment compared to non-operated controls or surgical controls \( (p > 0.05) \) (Fig. 4a and b).

There were no significant differences in protein levels in the fat pad due to small sample sizes and large variability; however, there were trends in the fat pad IL-1\( \beta \) protein levels which were lower in the DEX animals than surgical controls, as was the ratio of IL-1\( \beta \)/IL-1Ra \( (p > 0.05) \). There were no differences in the levels of bFGF, IL-1Ra, IL-6, IL-8, or TGF\( \beta \) between groups \( (p > 0.05) \).

**DISCUSSION AND CONCLUSIONS**

Corticosteroids have been used in the management of OA for over four decades. They are part of the practice guidelines for treatment of OA and have been proven to be safe and efficacious for pain relief.
and functional improvements in OA patients both short term\textsuperscript{16} and long term\textsuperscript{17,18}. Corticosteroids are also widely used for treatment in inflammatory conditions, such as rheumatoid arthritis (RA), lupus, and inflammatory bowel disease. Therefore, much work has been done on their role in modifying inflammation in OA. The majority of the work, however, has been done either in in vitro models, or in models inducing joint inflammation with chemical mediators.

Our study is the first to demonstrate a chondroprotective effect of dexamethasone in a non-mechanical surgical model of PTOA\textsuperscript{9}. Dexamethasone treatment has been previously shown to have a chondroprotective effect in vitro by completely blocking TNF\textsubscript{\alpha} induced GAG loss\textsuperscript{8}. We were able to alter inflammatory cytokines and gene expression in synovium and prevent both gross and histological cartilage damage caused after surgery with repeated high dose intra-articular dexamethasone injections post-injury. We hypothesized that a short-course of repeated high dose intra-articular injections of dexamethasone would diminish joint inflammation and thus change joint tissue catabolism and anabolism preventing post-traumatic cartilage damage. Our results support this hypothesis since treatment with dexamethasone after surgery significantly reduced the amount of cartilage damage compared to the surgical control animals. We were clearly able to show that 3 weeks of dexamethasone treatments elicited less gross joint damage and significantly lowered cartilage damage as seen by Mankin scores. This is consistent with previous work showing that treatment with dexamethasone in TNF\textsubscript{\alpha}-induced OA in vivo\textsuperscript{19}, mechanical injury + TNF\textsubscript{\alpha} + IL-6 induced OA in vitro\textsuperscript{8}, and IL-6 induced OA in vitro\textsuperscript{20} prevents glycosaminoglycan loss, prevents aggrecan degradation and increases proteoglycan synthesis. Furthermore work by Livne et al\textsuperscript{21} demonstrated that dexamethasone stimulated chondrocyte proliferation and rejuvenated the chondrocyte population in the mandibular condyles of old mice. Despite some in vitro evidence that glucocorticoids might be chondrotoxic\textsuperscript{22,23}, our work and other in vivo studies suggest that dexamethasone can regulate the catabolic effects of cartilage post-trauma.

In addition to chondroprotective effects of dexamethasone in this model, we also showed changes in synovial markers of inflammation, fibrosis, and degradation. Vento et al\textsuperscript{24} found that when treating synovial tissue cultured from OA patients with dexamethasone there was a reduction in synovial fibroblasts and morphological changes. We were unable to find any histological decrease in cell number with dexamethasone treatment compared to surgical controls. It is possible that 3 weeks is too late to see acute inflammatory proliferation from the injury, and too late for remodeling of the membrane and therefore we may have simply missed the window to see these changes histologically. Despite no histological evidence of changes in inflammation, there was a significant decrease in the expression of synovial IL-1\beta expression.
and protein levels with dexamethasone. IL-1β is thought to be involved in the development of OA with an acute inflammatory event, and induces COX2 as well as activates MMPs. Dexamethasone suppresses IL-1β therefore decreasing COX2 in RA synovium. It also inhibits chondrocyte MMP production in IL-1β stimulated cultures. While we found a down-regulation of synovial IL-1β, no other inflammatory cytokines were suppressed with dexamethasone. Synovial collagen I expression was suppressed by dexamethasone; we suspect that dexamethasone inhibited fibroblast proliferation that increases synovitis and fibrosis after injury preventing a destructive environment.

Synovial MMP3 is up-regulated in various models of OA and has been correlated to more severe radiographic OA. It degrades collagen type II, III, IV, IX, and X, as well as proteoglycans, laminin, elastin, and fibronectin all important in the integrity and architecture of the joint structures. While not significant, we found a trend for dexamethasone to decrease the expression of synovial MMP3. No other MMPs had lower expression with treatment, despite the mechanism MMP3 has on activating other MMPs. It is possible that the levels of MMP3 were not high enough to activate the other MMPs.

In addition to the role of synovium in OA several theories suggest that the fat pad may play a role in OA. Obesity predisposes patients to OA; traditionally this was thought to be because of increased joint loading, however, new evidence suggests that part of the pathogenesis may be due to increased fat pad leading to increased joint inflammation. Therefore we hypothesized that increased inflammation of the fat pad would be present in PTOA and that this would be suppressed by dexamethasone. This theory was supported by evidence showing an increase in IL-8 protein with immunohistochemistry in surgical controls. There was a non-significant decrease in IL-8 protein levels with dexamethasone. IL-8 is a potent chemokine which increases the inflammatory environment by attracting white blood cells and stimulating interleukin production and release. However, there was a significant increase in IL-8 expression of the right surgical limb in dexamethasone treated animals; we suspect this may be due to variability between animals due to the small sample size. The fat pad also had increased protein levels of MAC387 a macrophage marker and IL-1β in surgical controls, and while not significant due to sample size and variability, dexamethasone appeared to lower the levels of these proteins. Unfortunately there was not enough protein in two of the animal samples, therefore all western blot data were done with an n = 4. There was also a decrease in the ratio of IL-1β/IL-1Ra in the fat pad with dexamethasone. This suggests that the fat pad plays an important role maintaining joint inflammation and dexamethasone has the potential to suppress this.

In addition to changes in inflammation of the fat pad there was increased expression of degradative markers and growth factors with surgery that was suppressed with dexamethasone. bFGF and MMP13 were significantly higher post-surgery. MMP13 cleaves collagen II and degrades aggrecan, collagen IV, and IX, while bFGF is a growth factor for angiogenesis secreted by adipocytes. Angiogenesis will increase blood into the joint, which leads to OA. Dexamethasone suppressed expression of both bFGF and MMP13, therefore protecting the knee. While not significant, dexamethasone also decreased MMP3 expression and TGFβ expression. Many studies have shown that the down-regulation of TGFβ contributes to OA; we previously demonstrated that TGFβ was up-regulated in PTOA and speculated that this was to compensate for the up-regulation of MMP13. Su et al. found that dexamethasone suppressed TGFβ in an in vitro model of OA by interfering with TGFβ signalling and inhibiting endogenous TGFβ.

At the dosages that were used in this study we found that dexamethasone caused weight loss and had systemic effects on several organ systems. The dosages used in this study were very high, and would not be used clinically; however, they were selected to prevent joint inflammation over the study course which proved effective. As we have been able to show that at these doses joint inflammation was prevented thereby protecting the knee it is important in future not only to assess lower, less frequent dosages, as well as longer term studies. It is of note that the animal groups were small; however, despite small sample sizes we were able to show significant differences.

In conclusion, our results demonstrated that administration of repeated high dose intra-articular injections of dexamethasone inhibits synovial inflammation and is chondroprotective in a model of PTOA for up to 3 weeks in vivo. However, our results also showed that the dosage and treatment regime used did have adverse systemic effects on the rabbits and thus would clearly not be advised for PTOA management in humans. It has nonetheless given us further insight into the role of inflammation in PTOA and provided new avenues for potential disease modifying treatments. In addition, we suggest early corticosteroid injections after an injury may prevent later cartilage damage and joint degeneration.

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REFERENCES


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