EXPERIMENTAL STUDY

Acta Orthop Traumatol Turc 2015;49(4):438–446
doi: 10.3944/AOTT.2015.14.0312

Comparison of the effects of chronic intra-articular administration of tenoxicam, diclofenac, and methylprednisolone in healthy rats

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Objective: Lyophilized drug manufacturing and intra-articular (IA) applications have increased to address gastrointestinal side effects resulting from chronic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for degenerative joint disease. Accordingly, we histologically examined joint and stomach tissues from rats to determine and compare the effects of long-term treatment with an IA corticosteroid (methylprednisolone acetate), lyophilized NSAID (tenoxicam), and non-lyophilized NSAID (diclofenac) following application to the knee joint.

Methods: One hundred Wistar albino rats were divided into 4 groups of 25 rats: control, methylprednisolone, tenoxicam, and diclofenac. Ten IA injections were administered at 1-week intervals. Rats were sacrificed at 48 h and 1, 2, 4, and 8 weeks after the tenth injection. Histomorphologically, knee joint samples were examined for osteoarthritic changes and stomach tissue samples for gastric changes.

Results: Unlike methylprednisolone, diclofenac and tenoxicam caused increased fibrosis and fibroblast production; furthermore, chronic methylprednisolone use had no negative effects on the synovium or cartilage.

Conclusion: Chronic tenoxicam and diclofenac use affects joints more negatively than chronic steroid treatment.

Keywords: Diclofenac; experimental study; intraarticular; methylprednisolone; tenoxicam.

Osteoarthritis (OA) is a condition that, despite having multiple etiologies, manifests as characteristic morphological changes and clinical progression. OA involves the articular cartilage, subchondral bone, ligaments, joint capsule, synovial membrane, and peri-articular muscles, leading to articular cartilage fibrillation, vertical clefts (between chondrocyte groups), and fissures.[1] Accordingly, pain and decreased joint function are common presentations.

Non-steroidal anti-inflammatory drugs (NSAIDs)

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Submitted: August 29, 2014 **Accepted:** November 15, 2014

Available online at
www.aott.org.tr
doi: 10.3944/AOTT.2015.14.0312
QR (Quick Response) Code

are used to decrease the severity of symptoms associated with OA. Accordingly, the risk of gastrointestinal damage resulting from chronic NSAID treatment for degenerative joint disease has led to the increased manufacture of lyophilized NSAIDs and the intra-articular (IA) use of NSAIDs.[2,3] Clinical trials have demonstrated a low incidence of systemic side effects from IA applications.[4] For example, a previous experimental study reported that although a single IA dose could cause inflammation, no cartilage pathology was observed with chronic use.[5] However, the existing data is not sufficient to determine whether repeated IA NSAID injections induce local cartilage damage. Regarding other treatments, IA corticosteroid treatment has been shown to acutely attenuate pain in many studies, but the capacity for chronic pain alleviation has not been established.[6] IA corticosteroids may worsen arthritic lesions by inhibiting cellular activity.[7]

In the present study, we investigated the detrimental effects of long-term treatment with an IA corticosteroid (methylprednisolone acetate), lyophilized NSAID (tenoxicam), and non-lyophilized NSAID (diclofenac) via histological examination of joint and stomach tissues in rats after IA injection to the knee joint.

Materials and methods

This study was approved by the local ethical committee. One hundred 3-month-old Wistar albino rats (both sexes; body weight: 250–300 g) were divided into 4 groups of 25 rats each, as described below. Each rat received a total of 10 IA injections at 1-week dosing intervals while under mild ether anesthesia. A sterile 0.1-mL injection volume was instilled using a 26-gauge needle and insulin injector. All injections were administered after skin disinfection with povidone–iodine. Experimental groups as follows:

1. Control group: Serum (0.1 mL) was injected into the right knee joint.
2. Methylprednisolone group: Methylprednisolone (1 mg) was injected into the right knee joint.
3. Tenoxicam group: Tenoxicam (1 mg) was injected into the right knee joint.
4. Diclofenac group: Diclofenac-Na (0.75 mg) was injected into the right knee joint.

Five rats from each group were sacrificed at 48 h and 1, 2, 4, and 8 weeks after the final injection. The rats were humanely euthanized with a lethal dose of intraperitoneal sodium pentothal. The treated knee joints were dissected from their muscular attachments and submerged in 10% formaldehyde solution for pathological examination. The contralateral knee and stomach were also sampled. All samples were randomly numbered and sent to the pathology department. Materials were fixed for 1 week before placement in a Shandon™ TBD-2™ Decalcifier (Thermo Fisher Scientific, Waltham, MA, USA) for 5 days. After decalcification, the samples were cut into 2-mm-thick sections with preserved tissue orientations, labeled with previously assigned random numbers by a pathology specialist, and subjected to joint space and synovial membrane evaluation. The samples were washed under running water for 3 h to clear away residual acid and subsequently placed in an automatic tissue processor (Shandon Excelsior ES; Thermo Fisher Scientific) for 13 h.

The tissues were subjected to the following processing steps: formaldehyde (30 min, 2 times), alcohol (60 min, 6 times), xylene (60 min, 3 times), paraffin (60 min, once), and paraffin (80 min, 2 times). Tissues were embedded in paraffin, and 2-µm-thick sections were prepared and stained with hematoxylin and eosin. The sections were subjected to a blinded pathological examination under light microscopy (Olympus Bx-50; Olympus Optical, Tokyo, Japan).

The histological evaluation parameters and grading were established by the pathologist-author (Midi A.) based on the basic changes formed during the inflammation and reparation period of the structures forming the joint and the stomach (Table 1 and 2).

While fibroblast condensation was evaluated objectively, the other parameters were evaluated subjectively.

Serial sections were performed and evaluated to differentiate between artifactual changes and fissure, erosion and subchondral cyst formation.

During examination of fibrosis in the left knee, particular attention was paid to the adipose tissue vessels and fibrosis. Fibrotic tissues continuous with tendons were not considered to be fibrosis.

Fisher's exact probability test was used for the intergroup comparisons of variables. Comparison of right and left knees of each group could not be performed due to limited number of subjects. Significance level was considered to be $p<0.05$ and two-sided. Analyses were performed online from website http://vassarstats.net.

Results

Macroscopically, none of the subjects developed septic arthritis and no degenerative knee joint changes or stomach hemorrhage were detected.

Knee – *Congestion:* A prominent increase was ob-

served in all groups after 48 h. Significant congestion persisted in the diclofenac group at 1 week, but was controlled in all other groups. Congestion decreased in all groups after weeks 2, 4, and 8.

Edema: There was no significant increase in any group.

Presence of neutrophils: The groups differed significantly in terms of the number of neutrophils ($p < 0.05$). Neutrophilic infiltration was observed more frequently in the fascia located between muscle layers distal from synovial membranes and around vessels distal from the injection site (patellar area). The numbers of neutrophils increased during the first 48 h in the control, diclofenac, and steroid groups (Figure 1a), and decreased at the other time periods. There was no increase in neutrophils in the tenoxicam group at any time point. The lack of neutrophils in the tenoxicam group at 48 h was significant when compared with the other groups.

Presence of lymphocytes: The groups also differed significantly in terms of the number of lymphocytes ($p<0.05$). Increased lymphocyte levels were observed in the tenoxicam and diclofenac groups at all time points, and these increases were significant at 48 h and 1 week (Figure 1b). In contrast, the lymphocyte numbers did not increase in the control and steroid groups, and the steroids actually suppressed lymphocyte infiltration.

Eosinophils, histiocytes, and plasma cells: No increases were noted in any group at any time point.

Synovial hyperplasia: The groups differed significantly with respect to synovial hyperplasia ($p<0.05$), which was observed only at in week 8 in the tenoxicam group.

Fibroblasts: The groups differed significantly with respect to fibroblast numbers ($p<0.05$). Although these numbers did not increase in the control or steroid groups, the tenoxicam and diclofenac groups had significantly elevated numbers of fibroblasts at all time points (Figure 2a–c).

Fibrosis: The groups differed significantly with respect to fibrosis ($p<0.05$), with results similar to those of the fibroblast evaluation. Fibrosis was detected significantly more prominently during the chronic phases (weeks 4 and 8) in the tenoxicam and diclofenac groups. In contrast, no fibrosis was noted in the steroid or control group.

There were no significant changes in the following pa-

Table 1. Evaluation parameters.

Parameters	
In the synovium	Congestion, edema, neutrophil, lymphocyte, eosinophils, histiocytes, plasma cell presence, synovial hyperplasia, fibroblast aggregation, fibrotic severity.
In the cartilage	Thickness, fibrillation, superficial layer loss, fissures, erosion and ulceration.
In the subchondral bone	Cyst formation and osteophyte formation.
In the stomach	Erosion/ulcer, inflammation, lymphoid aggregates, activity (neutrophil presence), congestion/hemorrhage.

Table 2. Parameter scoring.

Parameters	**1**	**2**	**3**
Knee			
Neutrophil, eosinophil, plasma cell presence	None	A few	Many
Lymphocyte presence	None	Lymphocytes are few in number or only in the perivascular area	Many lymphocytes or aggregates are present.
Congestion, edema, synovial hyperplasia, cartilage thickness, fibrillation, surface layer loss, fissure formation, cyst formation, osteophyte formation, erosion (ulceration)	None	A few	Many
Fibrosis	None	Mild	Prominent
Fibroblast aggregation: average number of fibroblasts in one high magnification (×400)	<40	40–100	>100
Gastric erosion/ulcer, inflammation, lymphoid aggregates, activity (neutrophil presence), congestion/hemorrhagia	None	Mild	Prominent

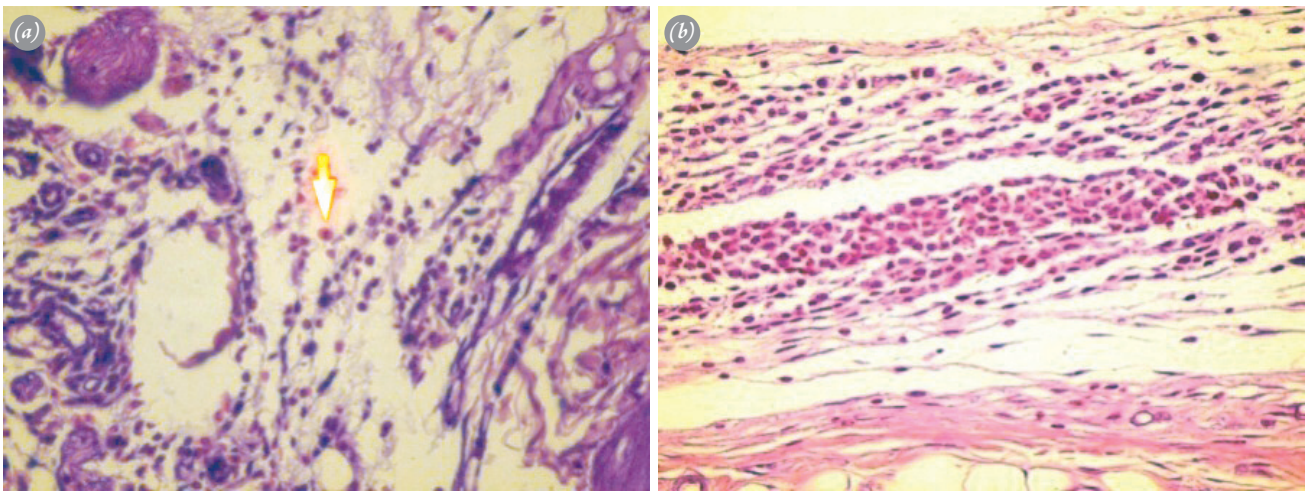

Fig. 1. **(a)** Presence of neutrophils at 48 h in the diclofenac group (hematoxylin and eosin, magnification: ×400). **(b)** Increased numbers of lymphocytes at 8 weeks in the tenoxicam group (hematoxylin and eosin, magnification: ×400). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

rameters: cartilage thickness, fibrillation, surface layer loss, fissures, cyst formation, osteophyte formation, and erosion/ulceration. Significant results are shown in Table 3.

No difference could be determined between groups regarding the investigation of the left knees.

Stomach – At 48 h: In contrast to the lack of inflammation in the control and steroid groups, significant levels were noted in the tenoxicam and diclofenac groups (Figure 2d, e). Activity and congestion were observed in the tenoxicam and diclofenac groups.

At 1 week: Inflammation was observed in all but the control group. Activity was observed in the tenoxicam and steroid groups.

Congestion was observed in the steroid group at 2, 4, and 8 weeks, and inflammation was observed in all groups except the control group. Significant results are shown in Table 4.

Discussion

In this study, we investigated the effects of OA treatments on joint and and stomach tissues collected from rats treated via IA injection. Notably, we did not observe any local side effects from the corticosteroid; in contrast, we observed and have described the local side effects of diclofenac and tenoxicam in the knee joint. In acute stage of systemic efficiency, while increased gastric ac-

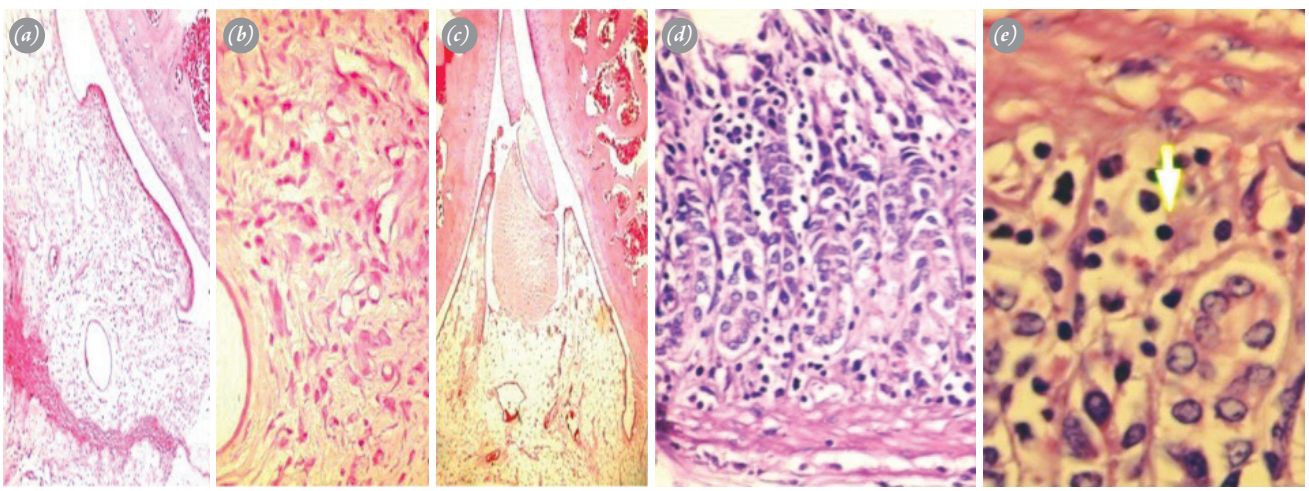

Fig. 2. Increased numbers of fibroblasts at 8 weeks in the tenoxicam **(a)** and diclofenac **(b)** groups (hematoxylin and eosin, magnification: ×100); **(c)** Tissue with a normal appearance in the steroid group (hematoxylin and eosin, magnification: ×100). Inflammatory cell infiltration in the stomach at 48 h in the tenoxicam group. (hematoxylin and eosin, magnification: ×400 and ×1000 in **(d)** and **(e)**, respectively). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

tivity was marked in tenoxicam and diclofenac groups, gastric activity in steroid group was similar to control group. Chronic effects of steroid usage was associated with more pronounced congestion in the stomach.

OA, the most frequent type of chronic arthritis, causes joint pain and dysfunction. Although there is no curative treatment for this disease, non-pharmacological methods (e.g., patient education, physical and occupational therapy) and pharmacological therapies, including non-opioid oral and topical (applied to the skin) analgesics, can be used for mild OA. IA injections of corticosteroid are recommended for patients with OA of the knee with joint effusion and local inflammation. Surgical treatments (e.g., osteotomy and joint arthroplasty), however, may be required in patients with severe symptoms.[8] Accordingly, the need for high doses of narcotic drugs during the postoperative period has led to the search for an alternative approach, and short-term IA NSAID therapy has been found to be efficient in patients with OA.

To further research in this area, Riggin et al.[9] studied the long-term effects of a single IA dose of ketorolac tromethamine in rat knees. The authors reported no negative histological effects on joint cartilage during an 84-day treatment period. Similarly, NSAIDs were not found to negatively affect joint cartilage. Nevertheless, increased numbers of fibroblasts, as well as increased fibrosis, were observed in the knee joints and were interpreted as chronic drug effects.

NSAIDs exert various effects on the joints. Some NSAIDs increase proteoglycan and hyaluronate (HA) production,[10] whereas others inhibit proteoglycan and collagen synthesis.[11] Some NSAIDs, such as indomethacin, induce interleukin-1 secretion by inhibiting the prostaglandin E2 production, which in turn inhibits cartilage matrix protein synthesis.[11] Additionally, COX-1 exerts negative effects on COX-2 by inhibiting apoptosis.[12] Other negative actions of NSAIDs include the inhibition of glycosyltransferase activity, uncoupling of mitochondrial oxidative phosphorylation, activation of cAMP-dependent kinase A, and disruption of protein–protein interactions at the cellular membrane.[12] Some NSAIDs, such as tiaprofenic acid, can suppress cartilage breakdown by inhibiting the degradation of aggregates in the cartilage. This effect is thought to associate with the inhibitory effect of these drugs on metalloproteinase activity.[13] Other drugs, such as nimesulide, protect against OA by inhibiting chondrocyte apoptosis.[12,14]

Tenoxicam has an analgesic effect when applied via IA after surgery.[2,3,15–18] Ozyuvaci et al. assessed the local effects of IA injections of tenoxicam on the cartilage and synovium in rats after 24 and 48 h and 7, 14, and 21 days. Grade 3 inflammation was observed at both 24 and 48 h; however, no inflammation was observed at later periods.[5] Similarly, Saricaoglu et al. applied IA lornoxicam at 1, 2, 7, 14, and 21 days and found no differences in inflammation.[19] Most earlier studies have focused on pain attenuation and the negative acute effects of tenoxicam in joints, whereas no studies have addressed chronic use. Accordingly, we investigated the effects of chronic IA tenoxicam use and observed increases in both fibrosis and fibroblast production. Significantly, however, neutrophils were not observed at 48 h in the tenoxicam group, in contrast to the other groups. Moreover, tenoxicam suppressed neutrophil infiltration, suggesting that the effects from recurrent use differ from the acute effects.

Diclofenac (an NSAID) is not administered via IA injection in clinical practice. As a result, there are no published data on IA diclofenac. In the present study, both IA diclofenac and tenoxicam increased fibrosis and fibroblast numbers after both acute and chronic use. Additionally, an increased number of neutrophils was observed only at 48 h in the diclofenac group, and no similar increases were observed in the tenoxicam group at any time point. No acute effects were observed with the repeated use of tenoxicam, and diclofenac exhibited acute efficacy.

When testing the safety of IA-injected substances, the chondrocyte is the most important cell to be considered.[20,21] In the present study, chondrocytes were evaluated according to several parameters, including cartilage thickness, fibrillation, surface layer loss, fissures, and erosion/ulceration. IA application of steroids is a supportive treatment for knee OA. While IA injections of corticosteroids have been used for a long time, the benefits and possible harmful effects of these agents are still controversial.[22] IA-injected corticosteroids can attenuate pain and improve function in the short term, but then pain attenuation effects of them diminish.[20,21] Repeated IA injections of corticosteroids can lead to progressive cartilage damage. Administration of injections at intervals of less than 3 months are not recommended.[20] Such injections have also been reported to increase the levels of synovial fibroblasts and collagen proteins in patients with OA.[23] Additionally, IA-injected corticosteroids can cause water retention, hyperglycemia, and hypertension if they pass from the joint into systemic circulation.[6,24,25] Pain attenuation effects of IA-applied corticosteroids have been emphasized in many studies.[4,26–33] Oral dexamethasone has been shown to repair cartilage in rats with arthrosis induced by an IA injection of zymosan.[34] Although the negative effects of single-dose steroid treatments in experimental studies have

Table 3. Statistically significant results from the knee analysis.

	Control (n=5)	Tenoxicam (n=5)	Diclofenac (n=5)	Steroid (n=5)	p
Duration: 48 hours					
Neutrophil, right					
None	1	5	0	3	
Few	1	0	2	1	0.006
Many	3	0	3	1	
Lymphocyte, right					
None	5	0	0	5	
Few	0	2	3	0	0.0001
Many	0	3	2	0	
Fibroblast (1 high-powered field), right					
<40,	5	0	0	4	
40–100	0	5	4	1	0.018
>100	0	0	1	0	
Fibrosis, right					
None	5	2	0	5	
Mild	0	3	4	0	0.001
Prominent	0	0	1	0	
Duration: 1 week					
Congestion, right					
None	0	5	1	5	
Mild	5	0	4	0	0.004
Prominent	0	0	0	0	
Lymphocyte, right					
None	5	1	2	5	
Few	0	3	3	0	0.001
Many	0	1	0	0	
Fibroblast (1 high-powered field), right					
<40,	5	2	1	5	
40–100	0	2	2	0	0.012
>100	0	1	2	0	
Fibrosis, right					
None	5	1	0	5	
Mild	0	2	3	0	0.008
Prominent	0	2	2	0	
Duration: 2 weeks					
Fibroblast (high-powered field), right					
<40,	5	3	1	5	
40–100	0	2	4	0	0.001
>100	0	0	0	0	
Fibrosis, right					
None	5	0	0	4	
Mild	0	3	3	1	0.005
Prominent	0	2	2	0	
Duration: 4 weeks					
Fibroblast (1 high-powered field), right					
40,	5	3	2	5	
40–100	0	2	3	0	0.002
>100	0	0	0	0	
Duration: 8 week					
Synovial hyperplasia, right					
None	5	2	5	5	
Mild	0	3	0	0	0.041
Prominent	0	0	0	0	
Fibroblast (1 high-powered field), right					
<40,	5	2	4	5	
40–100	0	3	1	0	0.03
>100	0	0	0	0	
Fibrosis, right					
None	5	0	0	4	
Mild	0	2	2	1	0.003
Prominent	0	3	3	0	

Table 4. Statistically significant results from the stomach analysis.

	Control (n=5)	Tenoxicam (n=5)	Diclophenac (n=5)	Steroid (n=5)	p
Duration: 48 h					
Inflammation					
None	5	0	0	5	
Mild	0	5	4	0	0.0001
Prominent	0	0	1	0	
Activity					
None	5	1	3	5	
Mild	0	4	2	0	0.024
Prominent					
Congestion					
None	5	0	2	5	
Mild	0	5	3	0	0.001
Duration: 1 week					
Inflammation					
None	5	0	1	0	
Mild	0	5	4	5	0.002
Prominent	0	0	0	0	
Activity					
None	5	0	4	1	
Mild	0	5	1	3	0.004
Prominent	0	0	0	1	
Congestion					
None	5	5	5	2	
Mild	0	0	0	3	0.035
Duration: 2 weeks					
Inflammation					
None	4	0	0	3	
Mild	1	4	5	2	0.03
Prominent	0	1	0	0	
Duration: 8 weeks					
Inflammation					
None	5	0	2	4	
Mild	0	4	3	1	0.02
Prominent	0	1	0	0	

been reported, several studies have described the positive effects of chronic steroid treatment on joint pain and range of motion. Furthermore, the study by Jaffre used ultrasonography to demonstrate the positive effects of oral dexamethasone use on joint cartilage in a rat model. Despite the absence of a histological study, the results of that study are consistent with those of our study in terms of the lack of an observed negative effect.

In the present study, the effect on the stomach and contralateral knee was investigated by us regarding systemic effects. While IA-injected methylprednisolone had similar effects with the control group regarding inflammation and congestion of the stomach at 48 hours and 1 week, it had lesser effects compared to the diclofenac and tenoxicam groups. Weight loss and louse infestation observed in the rats administered methylprednisolone is possibly due to side effects of synovial corticosteroid absorption in our study. However, severe gastritis (erosive, hemorrhagic, ulceration) was not determined in any group, and no negative effects on the contralateral knee was detected. Additionally, the present study is limited by the fact that the effects of chronic use of these drugs on knee cartilage were not explored in an experimental knee OA rat model.

In conclusion, we investigated whether the chronic use of various drugs (methylprednisolone, tenoxicam, and diclofenac) would have negative effects on healthy joints. We found that repeated methylprednisolone in-

jections did not cause chronic changes in the joints. As increased fibroblast numbers and fibrosis levels were observed in knee joint following IA tenoxicam and diclofenac treatment, multiple IA treatments may be harmful to the joint.

Conflics of Interest: No conflicts declared.

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