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Evaluation of the Potential Effects of Intra-Articular Rifamycin SV Injection into the Knee Joint on Articular Cartilage and Synovial Membrane

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ABSTRACT

Introduction: Rifamycin is widely used as a broad-spectrum antimicrobial agent; recent studies have demonstrated the anti-inflammatory properties of rifamycin SV. Our study aimed to determine the adverse effects of intra-articular injection of rifamycin SV on the articular cartilage and synovial membrane of the knee joint.

Methods: Thirty-two Wistar albino male rats were assigned to experimental and control groups (n=8 per group). On the first day, a single dose of 5mg/kg rifamycin SV (Rif; Koçak Farma, Türkiye) was injected into the right knee of the rats in the experimental groups (E1/E2), and a single dose of 0.9% isotonic sodium solution was injected into the right knee of the rats in the control groups (C1/C2). E1 and C1 rats were euthanized on the 7th day, and E2 and C2 rats were euthanized on the 28th day. Macroscopic and histopathological evaluations of the articular cartilage structures and synovial inflammation were performed. The histopathological grading and staging system of the Osteoarthritis Research Society International was used to evaluate the cartilage structures, with $p<0.05$ considered statistically significant.

Results: There were no statistically significant differences between the E1 and C1 groups or between the E2 and C2 groups in cartilage damage degree, stage, or score on the 7th day (p=0.117, p=0.197, p=0.197) and on the 28th day (p=0.077, p=0.061, p=0.062). When the E1 and C1 groups were examined to determine degrees of synovial inflammation, inflammation was significantly more common in the rifamycin SV (E1) group ($p<0.001$ on day 7). In contrast, degrees of synovial inflammation did not differ significantly between the E2 and C2 groups (p=0.256, day 28).

Conclusion: The intra-articular administration of rifamycin SV did not have a negative effect on articular cartilage but increased synovial inflammation on the 7th day.

Keywords: Rifamycin, knee, cartilage, isotonic sodium chloride

Introduction

Rifamycins are a group of antimicrobial drugs first discovered by Sensi at the Dow-Lepetit Research Laboratory in 1957 (1). Streptomyces mediterranei, a new Actinomyces strain isolated from a soil sample, produces molecules that primarily inhibit Gram-positive bacteria during culture. These molecules were named rifamycin A, B, C, D, and E and defined as the rifamycin complex family (2).

Rifamycins are broad-spectrum antimicrobial agents widely used to treat bacterial infections. However, recent studies indicate that rifamycin SV has anti-inflammatory and cellular protective properties (3,4). The anti-inflammatory effect of Rifamycin SV on neutrophils was also determined *in vitro* in the literature (5).

Septic arthritis is an infection of the joints. Diagnosis is made by clinical findings, gram staining, and culture of joint fluid (6). The most frequently detected pathogen is *Staphylococcus aureus* (7). Although the gold standard for treatment is surgical drainage and systemic antibiotics, arthroscopic lavage has also been described (8). In the case of inadequate treatment, cartilage damage develops, leading to permanent orthopedic sequelae. Therefore, evaluating the effect of rifamycin SV on knee joint cartilage may be important to determine its usefulness as a potential therapeutic strategy for septic arthritis.

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The aim of this experimental animal study was to determine the adverse effect of the intra-articular administration of rifamycin SV on knee joint cartilage, assessed by histopathological analysis.

Methods

Ethical approval was taken for our study from the İstanbul University Animal Experiments Local Ethics Committee (decision number: 2021/17, date: 30.04.2021). The experimental part of the study was carried out at İstanbul University, the Department of Experimental Animals. The study was conducted as part of a master's thesis at İstanbul University, Institute of Health Sciences, Department of Experimental Animal Science. All experimental animals used in our study belong to İstanbul University, and the necessary permissions have been obtained for their use. The study was conducted in accordance with the ARRIVE guidelines.

Thirty-two *Wistar albino* male rats, 9-10 months old and weighing 380-420 g, were used in the study. All animals were numbered by making small ear incisions. The subjects were randomly divided into four groups of eight rats each. Randomization was performed using a table of random numbers. Two groups were designated experimental: experimental group 1 (E1) and experimental group 2 (E2). The other two groups were designated control groups 1 (C1) and 2 (C2). The groups of animals were written on labels attached to their cages. During the study, the rats were provided with a standard laboratory rodent pellet diet (ad libitum) and free access to water. The animals were housed in appropriate cages under standard room conditions with a 12-hour night, 12-hour day rhythm at a temperature of 21±2 ^{0}C and a humidity level of 55±10%. On the first day, a single dose of rifamycin SV (Rif; Koçak Farma, Türkiye) at 5 mg/kg was injected into the right knee of the rats in the experimental groups (E1, E2), and a single dose of 0.9% isotonic sodium chloride (20 microliters; Polifleks; Polifarma, Türkiye) was injected into the right knee of the rats in the control groups (C1, C2). Rifamycin SV dose was determined based on previous animal experiments in the literature (9). An intra-articular injection was administered into a normal cartilaginous knee joint. No prior pathology was identified.

Animals in the E1 and C1 groups were euthanized at the end of the 7th day, and animals in the E2 and C2 groups at the end of the 28th day. Euthanasia was performed by administering pentothal at a high dose (200 mg/kg). After euthanasia, the right lower extremities of the subjects were removed by hip disarticulation following appropriate antisepsis and preparation. Muscle tissues were separated. The right femur and tibia were preserved together with the knee joint ligaments and placed individually in appropriately labeled sample containers containing 10% formaldehyde solution. The samples were then delivered to the pathology laboratory for histopathological examination.

Injection Technique

Before the procedures, all animals were weighed and their weights recorded. For anesthesia, 5 mg/kg xylazine hydrochloride (Rompun; Bayer Healthcare, Leverkusen, Germany) and 50 mg/kg ketamine hydrochloride (Ketalar; Pfizer, Türkiye) were administered intraperitoneally. Ethical rules and animal welfare are at the forefront of experimental animal studies. Intra-articular injections were administered under anesthesia to ensure that the animal did not experience pain and that the delicate injection could be performed in accordance with the technique. Then, the right knees of the animals were shaved while the animals were in the supine position. The patella, patellar tendon, and tibial tuberosity were marked on the skin with a skin pencil. Skin antisepsis was performed using 10% povidone-iodine (Batticon; Adeka, Türkiye). Injections were administered via the transpatellar route (the same route of drug administration when needed), midway between the patella and the tuberosity of the tibia, using tuberculin syringes with a 26G needle tip. All animals in the experimental groups (E1 and E2) were injected with 5mg/kg of rifamycin SV (Rif; Koçak Farma, Türkiye), and those in the control groups (C1 and C2) were injected with 0.9% isotonic sodium chloride (20 microliters). When the anesthesia had completely taken effect, the subjects were allowed to bear weight and move freely in the cage. The criteria we used in the study to decide that the effect of anesthesia has ended are: return of reflex responses (pedaling, tail pinching, etc.), the animal regains its righting reflex, return of coordinated movements, and the animal becomes fully conscious (10). Because knee movements might be affected and gait disorders might develop following the injections, housing and care were provided for each experimental and control animal in a cage. After 24 hours, all subjects were active, showed no signs of pain, and they were moved to cages housing four animals each.

Macroscopic Evaluation

In macroscopic examination, knee joint cartilages were stained with Indian ink and evaluated for possible damage according to the criteria defined by Yoshioka et al. (11) (Table 1). To ensure blinding during macroscopic examination, the specimens were numbered and sent to the examiner. The examination was performed by a researcher who was not involved in the experimental procedures.

Histopathological Evaluation

Specimens containing femora and tibiae with preserved knee joints were decalcified in 20% hydrochloric acid for microscopic examination. Afterward, 5-micrometer-thick longitudinal sections were taken perpendicular to the joint surface using a microtome. Staining was performed using hematoxylin-eosin and safranin O, and the stained specimens were examined under a light microscope (Olympus®

Table 1. Classification of macroscopic evaluation of cartilage damage defined by Yoshioka et al. (11)

Grade	Macroscopic changes
1	İntact surface: surface appears normal and does not retain any ink;
2	Minimal fibrillation: site appears normal before staining, but retains the India ink as elongated specks or light gray patches;
3	Overt fibrillation: the cartilage is velvety in appearance and retains ink as intense black patches;
4	Erosion: loss of cartilage exposing the underlying bone.

BX51-x100). For the evaluation of the cartilage structures, the cartilage histopathological grading and staging system of the Osteoarthritis Research Society International (OARSI) was used (12) (Tables 2 and 3). In this system, cartilage damage is graded and staged, and the osteoarthritis score is calculated by multiplying the assigned grade and stage values. Histopathological evaluation of synovial inflammation was evaluated according to the 5-point scale defined by Ozyuvaci et al. (13) (Table 4).

To ensure blinding of the histopathological evaluation, specimens were sent to the laboratory with animal numbers. Histopathological examination of all samples was performed by a single pathologist.

Statistical Analysis

The SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) program was used for statistical analysis, and the G Power 3.1.9.7 (Franz Faul, Germany) program was used for sample calculation.

Based on the calculation using the determined effect size (d: 0.849), 95% power, and a 5% margin of error, a total of at least 32 samples should be studied.

Table 2. Cartilage damage histopathological statiging criterias according to OARSI classification (12)

Stage	% involvement (surface, area, volume)
0	No osteoarthritis activity seen
1	<10%
2	10-25%
3	25-50%
4	>50%

Comparisons between cartilage scores and degrees of synovial inflammation were conducted using the Mann–Whitney U test. $p<0.05$ was used as the level of significance.

Results

No animal deaths were reported during the study. No problems with independent mobilization of the experimental animals were observed, and no post-injection infections occurred.

Macroscopic Findings

According to the evaluation results using the macroscopic classification ve cartilage damage defined by Yoshioka et al. (11), no difference was detected between the E1 and C1 groups consisting of rats euthanized at the end of the 7th day ($p=0.535$). No difference was observed in the degree of cartilage damage between the E2 and C2 groups, which consisted of rats euthanized at the end of day 28 ($p=0.268$).

Histopathological Findings

According to evaluation using the OARSI cartilage histopathological grading and staging system, no difference was detected in the degree of cartilage damage between the E1 and C1 groups, which consisted of rats euthanized at the end of day 7 ($p=0.117$). No difference was detected in cartilage damage stages or cartilage scores (both $p=0.197$) (Table 5; Figures 1 and 2). No difference was observed in the degree of cartilage damage between the E2 and C2 groups; both groups consisted of rats euthanized at the end of day 28 ($p=0.077$). No differences were detected with respect to cartilage damage stages ($p=0.061$) or cartilage scores ($p=0.062$) (Table 5, Figures 3 and 4).

When the E1 and C1 groups, consisting of rats euthanized on day 7, were compared for the degree of synovial inflammation, the group

Table 3. Cartilage damage histopathological graiding criterias according to OARSI classification (12)

Grade	Macroscopic changes
Grade 0: surface intact, cartilage morphology intact	Matrix: normal architecture Cells: intact, appropriate orientation
Grade 1: surface intact	Matrix: superficial zone intact, oedema and/or superficial fibrillation (abrasion), focal superficial matrix condensation Cells: death, proliferation (clusters), hypertrophy, superficial zone Reaction must be more than superficial fibrillation only
Grade 2: surface discontinuity	As above + Matrix discontinuity at superficial zone (deep fibrillation) ± Cationic stain matrix depletion (Safranin O or Toluidine Blue) upper 1/3 of cartilage ± Focal perichondronal increased stain (mid zone) ± Disorientation of chondron columns Cells: death, proliferation (clusters), hypertrophy
Grade 3: vertical fissures (clefts)	As above Matrix vertical fissures into mid zone, branched fissures ± Cationic stain depletion (Safranin O or Toluidine Blue) into lower 2/3 of cartilage (deep zone) ± New collagen formation (polarized light microscopy, Picro Sirius Red stain) Cells: death, regeneration (clusters), hypertrophy, cartilage domains adjacent to fissures
Grade 4: erosion	Cartilage matrix loss: delamination of superficial layer, mid layer cyst formation Excavation: matrix loss superficial layer and mid zone
Grade 5: denudation	Surface: sclerotic bone or reparative tissue including fibrocartilage within denuded surface. Microfracture with repair limited to bone surface
Grade 6: deformation Bone	Bone remodelling (more than osteophyte formation only). Includes: microfracture with fibrocartilaginous and osseous repair extending above the previous surface

Table 4. Grading of histopathological inflammatory changes in the knee joints of rats (13)

Grade	Histopathological changes
1	No inflammation
2	Minimal inflammation: mild congestion and oedema
3	Mild inflammation: erosion of joint surface, congestion and oedema, small number of neutrophils
4	Moderate inflammation: neutrophils and macrophages, synoviocyte hyperplasia
5	Severe inflammation: neutrophils and macrophages, synoviocyte hyperplasia, fibrin exudation

administered rifamycin SV exhibited greater synovial inflammation ($p<0.001$) (Table 6 and Figure 5). When the E2 and C2 groups, rats euthanized at the end of day 28, were compared with respect to degrees of synovial inflammation, no difference was detected between the two groups ($p=0.256$) Table 6.

Discussion

Rifamycins are a family of antimicrobials that act by inhibiting RNA polymerase. Rifamycin SV is an antimicrobial of the rifamycin group that was first used therapeutically. In addition to their antimicrobial activity, rifamycins have been reported to exert anti-inflammatory effects. It has been determined that these effects are exerted by inhibiting the synthesis of cytokines from THP-1-type monocytes and macrophages activated by lipopolysaccharide (LPS) (4). Rifamycins have also been shown to antagonize tumor necrosis factor alpha and LPS-induced nuclear factor kappa B activities and inhibit inflammatory chemokines and interleukin (IL)-8 synthesis induced through IL-1β (3).

Rifamycins are antibiotics that can be used orally or parenterally. However, the literature reports various local uses. Bruni et al. (14) reported positive results using rifamycin SV topically in the treatment of herpes zoster. Boztaş et al. (15) used rifamycin SV locally in the treatment of pilonidal sinus disease and found that it was beneficial to the treatment. For this reason, intra-articular injection was used as a alternative mode of administration in our study.

The starting point of our study was the question of whether rifamycin is safe for intra-articular use to treat intra-articular infections, because it is a broad-spectrum antimicrobial agent with anti-inflammatory effects. A review of the literature identified several studies on the intra-articular administration of rifamycins. Rifamycins were first used intra-articularly to treat rheumatoid arthritis. In a randomized, prospective study, patients with rheumatoid arthritis received a total of 525 mg of rifamycin intra-articularly once weekly for 10 weeks. In clinical findings, a significant improvement in erythrocyte sedimentation rate and C-reactive protein level was detected (16). A literature review examining 20 years of data stated that intra-articular rifamycin was effective against active synovitis and could be used together with slow-acting antirheumatic drugs (17). Rifamycin SV was compared with triamcinolone acetonide in a randomized controlled trial involving 87 patients with rheumatoid arthritis and refractory knee synovitis. It was concluded that rifamycin SV was less useful than triamcinolone acetonide in the local treatment of rheumatoid synovitis (18). In a different study, the application of rifamycin to the joint was shown to be effective in reducing pain in rheumatoid arthritis patients (19).

Rifamycins have also been used intra-articularly in the treatment of hemophilic arthropathy. A 2018 Korean study showed that chemical synovectomy with rifamycin could prevent hemarthrosis and improve clinical symptoms in patients with hemophilia. It has been found that rifamycin protects the joint, especially in the early stages of arthropathy, where there is no narrowing of the joint space (20). In 2021, Caviglia et al. (21) examined the use of intra-articular rifamycin in the treatment of hemophilic arthropathy. It has been stated that rifamycin is more effective when used in small joints (elbow and ankle) than in larger joints (knee) and that multiple injections predict failure (21).

Studies have shown that application of rifamycin to the joint reduces inflammation in rheumatological diseases and intra-articular bleeding

Table 5. Histological findings of OARSI assessment

OARSI Scores		Groups									
		E1		C1		p	E2		C2		p
		n	%	n	%		n	%	n	%	
Grade	0	4	50	7	87.5	0.117	2	25	6	75	0.077
	1	4	50	1	12.5		4	50	1	12.5	
	2	0	0	0	0		1	12.5	1	12,5	
	3	0	0	0	0		1	12.5	0	0	
Stage	0	4	50	7	87.5	0.197	2	25	6	75	0.061
	1	4	50	0	0		3	37.5	1	12.5	
	2	0	0	1	12.5		2	25	1	12.5	
	3	0	0	0	0		1	12.5	0	0	
Score	0	4	50	7	87.5	0.197	3	37.5	6	75	0.062
	1	4	50	0	0		2	25	1	12.5	
	2	0	0	1	12.5		1	12.5	0	0	
	4	0	0	0	0		0	0	1	12.5	
	6	0	0	0	0		2	25	0	0	

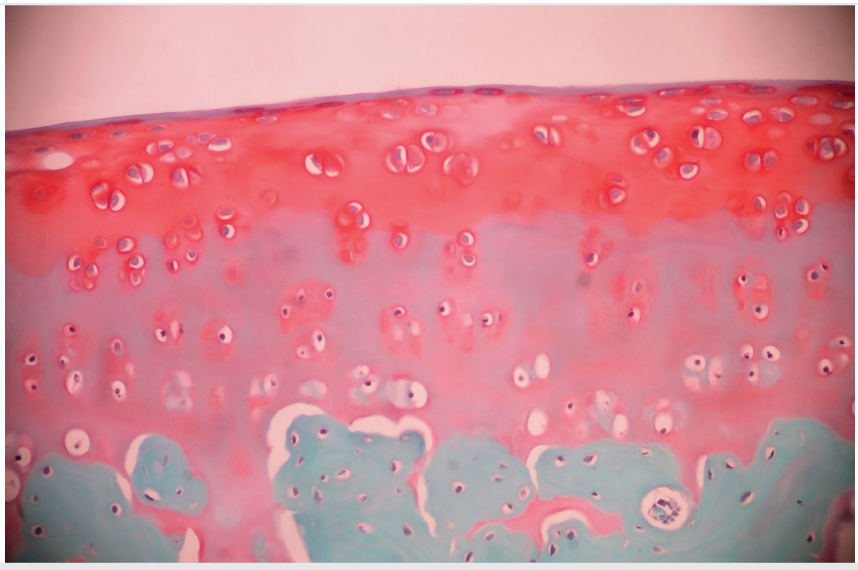

Figure 1. Histopathological appearance of the sample with grade 0 cartilage damage in group C1 (safranin-0 x100-normal architecture)

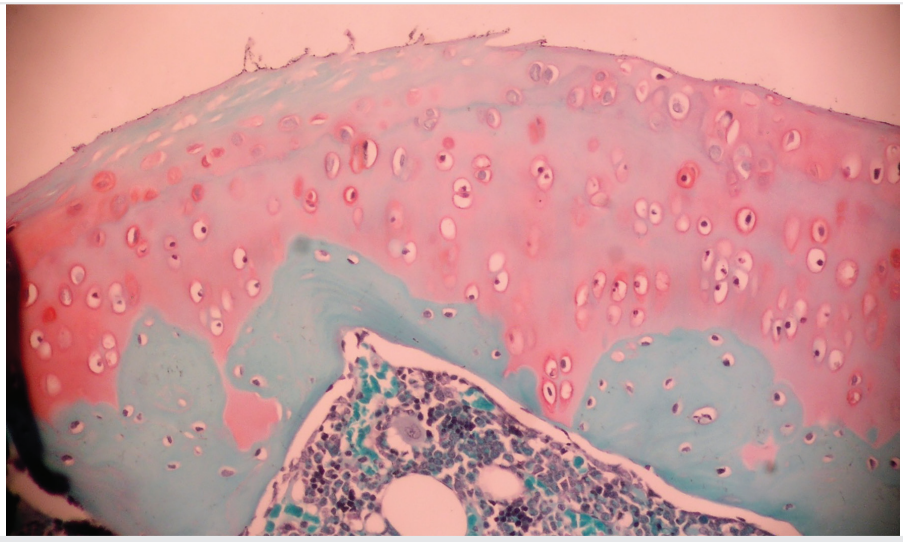

Figure 2. Histopathological appearance of the sample with grade 1 cartilage damage in group E1 (safranin-0 x100-superficial fibrillation)

in hemophilic patients. However, because cartilage destruction in these diseases appears to result from the underlying disease process, these studies do not demonstrate whether rifamycins have beneficial or harmful effects on cartilage or whether they are reliable.

In our study, cartilage structures in rats were examined using the OARSI scale after intra-articular application of rifamycin SV. This scale is a rating, staging, and scoring method (12). The animal selection and scale used were compatible with similar cartilage studies in the literature (22).

The intra-articular injection volume to be administered to rats is also important. Excessive application can damage the joint capsule and may result in drug extraction. In such cases, the effects of the drug may not be clearly observed, and additional complications may occur. Since a study conducted on this subject in the literature determined that a maximum of 30 microliters could be injected into the rat knee, 20 microliters was used as the injection volume in our study (23). Rifamycin SV is red. On macroscopic examination after euthanasia, no red discoloration was observed in the subcutaneous tissue of any sample.

The administered drug dose was determined based on previous studies. Lee et al. (9) studied a rabbit hemophilic arthropathy model and injected 10 mg rifamycin into the knees in 2000-g rabbits. In our study, the dose applied was 5 mg/kg.

Starting from a hypothesis similar to our study, Kwon et al. (24) examined the intra-articular application of rifamycin in MRSA septic arthritis. The authors stated that the local application of rifamycin may be a promising new therapeutic strategy for septic arthritis, due to the simultaneous alleviation of intra-articular inflammation and targeting of intracellular bacteria.

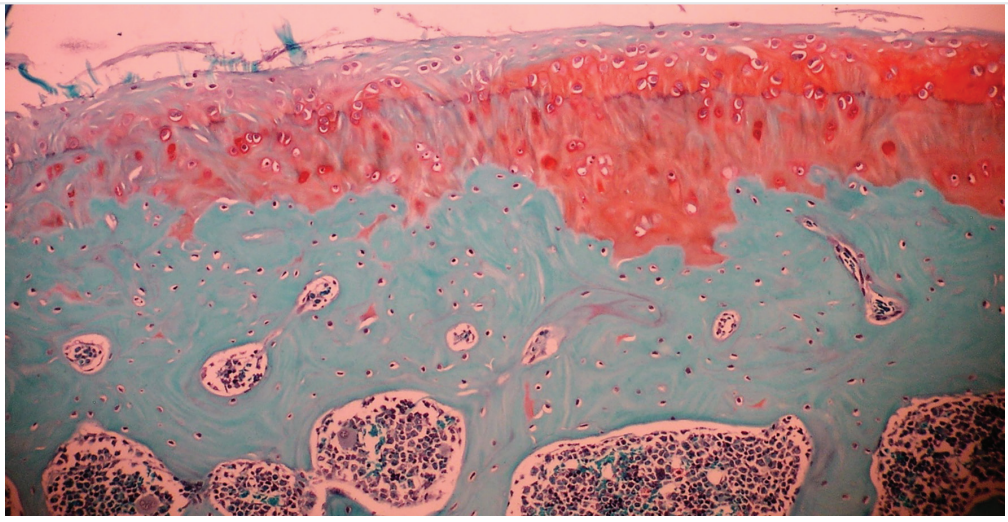

Figure 3. Histopathological appearance of the sample with grade 2 cartilage damage in group C2 (safranin-0 x100-superficial zone deep fibrillation)

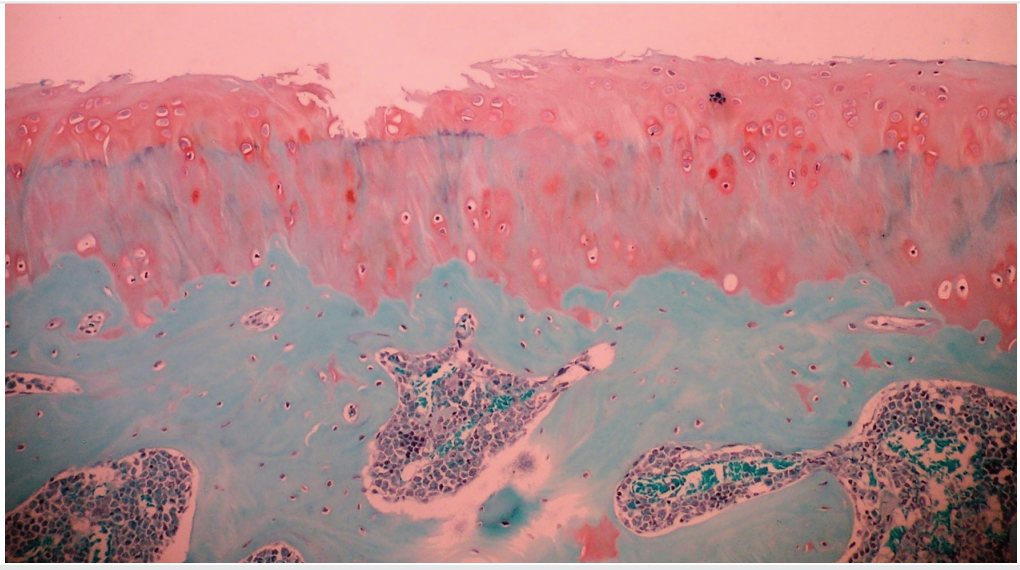

Figure 4. Histopathological appearance of the sample with grade 3 cartilage damage in group E2 (safranin-0 x100-matrix vertical fissures into mid-zone)

Table 6. Histological findings of synovial inflammation

Synovial inflammation		Groups									
		E1		C1		P	E2		C2		p
		n	%	n	%		n	%	n	%	
Grade	1	0	0	8	100	<0.001	3	37.5	6	75	0.256
	2	6	75	0	0		5	62.5	1	12.5	
	3	2	25	0	0		0	0	0	0	
	4	0	0	0	0		0	0	1	12.5	
	5	0	0	0	0		0	0	0	0	

Study Limitations

The most important limitation of our study is reliance solely on macroscopic and histopathological examinations for evaluation. The viability of cartilage cells could have been examined in the context of cartilage injury. In addition, immunohistochemical examinations and assessments of inflammatory markers to evaluate synovitis would have strengthened the study. However, these examinations could not be performed due to funding limitations. Furthermore, histopathological and macroscopic examinations were performed by a single researcher. Interobserver reliability was not investigated.

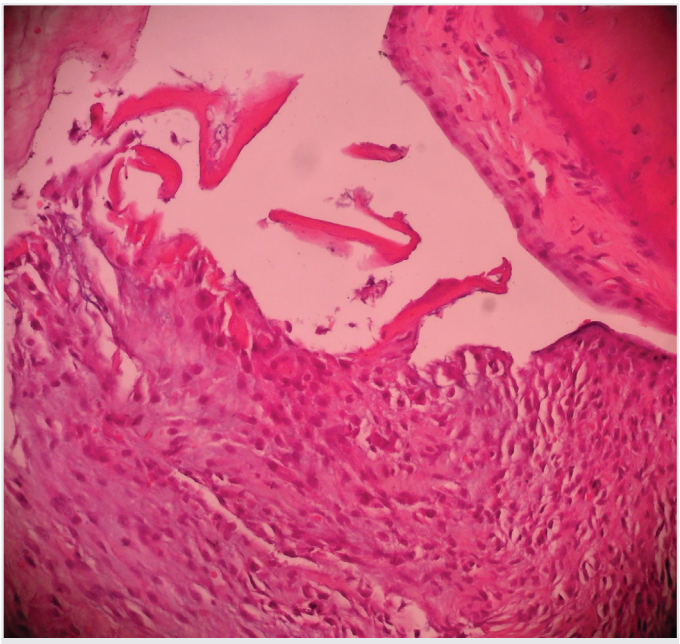

Figure 5. Histopathological appearance of the sample with grade 3 synovial inflammation in group E1 (hematoxylin eosin x100-mild synovial hyperplasia, increased vascularity, congestion, presence of rare neutrophils, focal fibrin exudation)

Conclusion

In our study, no significant difference in cartilage damage was detected compared with the control group during both the early and late periods, and intra-articular rifamycin SV was shown to be safe. However, a significant increase in synovial inflammation was observed early in the group that received rifamycin SV. Therefore, studies are needed to evaluate the reliability of rifamycin use in treating diseases that cause additional synovial inflammation, such as septic arthritis.

Ethics

Ethics Committee Approval: Ethical approval was taken for our study from the İstanbul University Animal Experiments Local Ethics Committee (decision number: 2021/17, date: 30.04.2021).

Informed Consent: Not applicable, as this study did not involve human participants.

Footnotes

Authorship Contributions: Surgical and Medical Practices - Y.B., F.B., İ.D., A.S.K.; Concept - Y.B., E.Ö., M.C., F.B.; Design - Y.B., E.Ö., M.C., F.B.; Data Collection or Processing - Y.B., M.C., İ.D., A.S.K.; Analysis or Interpretation - Y.B., E.Ö., İ.D., A.S.K.; Literature Search - Y.B., M.C., İ.D., A.S.K.; Writing - Y.B., F.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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