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Artículo original

Evaluación histopatológica comparativa de terapias intraarticulares en un modelo experimental de osteoartritis

Comparative histopathological evaluation of intra-articular therapies in an experimental model of osteoarthritis

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Palabras clave: osteoartritis; histología; preparaciones farmacéuticas

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RESUMEN

Objetivos: evaluar histopatológicamente la osteoartritis tratada con diferentes fármacos intraarticulares en ratas, comparando plasma rico en plaquetas (PRP), ácido hialurónico (AH), sulfato de condroitina y triamcinolona.

Materiales y métodos: osteoartritis inducida en 30 ratas Wistar mediante inyección de zimosán. Se formaron cinco grupos (n=6): PRP, AH, condroitina, triamcinolona y control. Los tratamientos se aplicaron cada 14 días por 60 días. Posteriormente se realizó eutanasia y análisis histopatológico del cartílago subcondral, evaluando estructura, condrocitos, sinovio e inflamación. Se aplicaron pruebas Kruskal-Wallis y Dunn-Bonferroni.

Resultados: animales con El PRP mostró condrocitos maduros en columnas y regeneración, con inflamación moderada. El AH presentó erosiones mínimas, úlceras superficiales, alta densidad celular y bajo índice inflamatorio, sugiriendo efecto condroprotector y antiinflamatorio. La condroitina preservó la tidemark, redujo flaps de cartílago y evidenció baja inflamación. La triamcinolona alcanzó mejor control inflamatorio, aunque con limitada regeneración. El control mostró daño moderado, alta inflamación y condrocitos desorganizados.

Conclusiones: PRP y AH demostraron mayor capacidad regenerativa: PRP favoreció maduración condrocitaria y AH redujo daño e inflamación. La triamcinolona destacó por efecto antiinflamatorio y la condroitina por perfil protector.

Conflictos de interés: *los autores declaran que no presentan conflictos de interés.*

Key words: *osteoarthritis; histology; pharmaceutical preparations.*

ABSTRACT

Objectives: *to perform a histopathological evaluation of osteoarthritis treated with different intra-articular drugs in rats, comparing platelet-rich plasma (PRP), hyaluronic acid (HA), chondroitin sulfate, and triamcinolone.*

Materials and methods: *osteoarthritis was induced in 30 Wistar rats by zymosan injection. Five groups were formed (n = 6): PRP, HA, chondroitin sulfate, triamcinolone, and control. Treatments were administered every 14 days for 60 days. Subsequently, euthanasia was performed, and histopathological analysis of the subchondral cartilage was conducted, evaluating structure, chondrocytes, synovium, and inflammation. The Kruskal–Wallis and Dunn–Bonferroni tests were applied.*

Results: *animals treated with PRP showed mature chondrocytes arranged in columns and signs of regeneration, with moderate inflammation. HA presented minimal erosions, superficial ulcers, high cellular density, and a low inflammatory index, suggesting both chondroprotective and anti-inflammatory effects. Chondroitin sulfate preserved the tidemark, reduced cartilage flaps, and exhibited low inflammation. Triamcinolone achieved better inflammatory control, although with limited regeneration. The control group showed moderate damage, high inflammation, and disorganized chondrocytes.*

Conclusions: *PRP and HA demonstrated greater regenerative capacity: PRP favored chondrocyte maturation, and HA reduced tissue damage and inflammation. Triamcinolone stood out for its anti-inflammatory effect, while chondroitin sulfate exhibited a protective profile.*

INTRODUCTION

Osteoarthritis (OA) is the most common and disabling joint disease, with high morbidity and significant impact on quality of life and global public health, particularly in older adults[1]. Current treatments mainly target pain relief and symptom control, with limited effect on disease progression[2]. A key challenge remains the unclear role of cartilage pathology in OA progression[2].

Pharmacological strategies include symptom- and disease-modifying agents. Symptom relief may involve joint aspiration and intra-articular injections[1]. Glucosamine and chondroitin are widely used chondroprotective compounds[3]. Hyaluronic acid (HA) improves synovial fluid viscosity, protects cartilage, reduces chondrocyte apoptosis, and modulates inflammation[4]. Triamcinolone hexacetonide (TH) provides short-term pain relief (<4 weeks) due to prolonged intra-articular retention[5,6].

Emerging orthobiologic therapies include bone marrow concentrate (BMC), mesenchymal stem cells (MSCs), and platelet-rich plasma (PRP)[7]. Autologous PRP offers growth factors with chondrogenic and anti-inflammatory potential, but evidence remains limited regarding formulations, protocols, and preparation methods[8].

MATERIALS AND METHODS

This study was an experimental, prospective investigation conducted on an animal model (rats). A total of 30 adult male Wistar rats (Rattus norvegicus albinus), weighing 280–300 g and aged 120 days, were obtained from the Anilab Animal Facility (Paulínia-SP, Brazil). The animals were housed in the animal facility of Faculdade Evangélica Mackenzie do Paraná under controlled conditions: temperature of 22°C, a 12-hour light-dark cycle, noise control, and humidity levels maintained between 40–60%. They were kept in Type III cages (three rats per cage) and provided with a standardized diet (Purina®) and water ad libitum throughout the experiment. All procedures adhered to ethical guidelines for the use of sentient animals in experimental research and commenced only after approval from the Institutional Animal Care and Use Committee (CEUA) under protocol 2023-000826.

On Day 0, all animals were anesthetized (as per the protocol detailed in section 3.1) and underwent arthrocentesis of the right femorotibial-patellar joint under aseptic conditions. A single intra-articular injection of 50 µL of Zymosan (Saccharomyces cerevisiae, Sigma Chemical Co.), dissolved in 10 mL of injectable water, was administered at a dose of

250 mg to induce experimental osteoarthritis. To confirm OA induction, radiographic projections were performed on Day 16.

The animals were then randomly assigned into five groups (n=6 per group), as per Karapolat (2008):

- Group 1 (PRP Treatment): Intra-articular injection of 0.2 mL of platelet-rich plasma (PRP) into the femorotibial-patellar joint every 14 days for 60 days. PRP was obtained by collecting blood from the external jugular vein, followed by centrifugation at 3,500 rpm for 9 minutes.
- Group 2 (Hyaluronic Acid Treatment): Intra-articular administration of 3 mg/kg of hyaluronic acid (Polireumin®) every 14 days for 60 days.
- Group 3 (Chondroitin Sulfate Treatment): Intra-articular administration of 5 mg/kg of chondroitin sulfate (Condroton®) every 14 days for 60 days.
- Group 4 (Triamcinolone Treatment): Intra-articular administration of 0.2 mg/kg of triamcinolone every 14 days for 60 days[9].
- Group 5 (Control Group): Intra-articular injection of 0.2 mL of sterile water every 14 days for 60 days.

On Day 60, all animals were euthanized following the protocol outlined in section 3.2. A biopsy punch was used to collect subchondral cartilage from the femorotibial-patellar joint. The samples were immediately fixed in 10% formalin for histopathological evaluation (detailed in section 3.3).

Anesthetic and analgesic protocols

The arthritis-inducing agent was administered under inhalation anesthesia with isoflurane (2–5% in oxygen). Induction was performed in a chamber until loss of vibrissae movement, then maintained via face mask. Animals were monitored post-procedure until recovery, confirmed by voluntary movements and ambulation.

Form of euthanasia

After 60 days, rats were euthanized with isoflurane inhalation, confirmed after 10 min without respiration[12]. Subchondral cartilage from the femorotibial-patellar joint was then collected for histopathological analysis.

Histopathological examination

Specimens were preserved in 10% formalin with 5% formic acid for 60 days, with solution changes every five days, then processed and stained with Hematoxylin-Eosin and Mallory's Trichrome. Histopathological evaluation included cartilage, chondrocytes, synovium, and inflammation. Cartilage was scored across 11 parameters (max 66) following Ostergaard et al.[13]. Chondrocytes were scored across five parameters15, with isogenous groups indicating regeneration. Synovium was assessed by eight parameters (36), and inflammation by four[10].

Injury scores

Right femorotibial-patellar joint samples were fixed in 10% formalin with 5% formic acid for 60 days, with solution changes every five days, then processed histologically. Serial 5-µm sections were stained with Hematoxylin-Eosin (H&E) and Mallory's Trichrome. Osteoarthritis (OA) severity was determined by cumulative scores for cartilage, chondrocytes, synovium, and lymphoplasmacytic inflammation with giant cells, providing a joint impairment index.

Cartilage was assessed through 12 parameters (score 1–12; total 66) based on Ostegaard et al., 1997. Chondrocytes were scored by five parameters (total 5), with isogenous groups indicating regeneration. Synovium was scored by eight parameters (total 36). Inflammation included four parameters (mild, moderate, severe, adjacent myositis; total 7).

Overall OA severity was classified on an ordinal scale (1–114), from mild to most severe.

Statistical methods

To assess treatment effects on histopathological indices (cartilage, chondrocytes, synovium, and inflammation), the Kruskal-Wallis test was applied, followed by Dunn's test with Bonferroni correction for pairwise comparisons[10,11]. The Kruskal-Wallis test, a non-parametric ANOVA, was chosen as it accommodates multiple independent groups. A significant result indicates variance differences among groups but not which ones; therefore, Dunn-Bonferroni identified specific group differences. Significance was set at $p < 0.05$.

Table: Classification of osteoarthritis severity based on histopathological scoring.	
Severity Classification	**Score**
Noteworthy changes absent (NDN)	1 – 15
Very Low Severity	16 – 31
Low Severity	32 – 47
Moderate Severity	48 – 63
High Severity	64 – 79
Very High Severity	80 – 95
Extreme Severity	96 – 114

RESULTS

Histopathology showed cartilage erosion and osteophytes in all groups. Distal femoral epiphysis biopsies (cartilage, chondrocytes, synovium, and inflammation) were all grade 6 by the Pritzker classification[14]. Cartilage regeneration, chondroprotection, and inflammation differed among groups: PRP and HA improved regeneration and chondroprotection despite persistent inflammation; triamcinolone had the greatest anti-inflammatory effect but poor regeneration; controls showed minimal regeneration, marked inflammation, and disorganized cells.

The untreated group showed the highest OA severity (Graph 1), indicating greater disease progression without treatment. Significant differences were observed between the Chondroitin and Untreated groups (p=0.014) and the Triamcinolone and Untreated groups (p=0.014) (Graph 2), demonstrating a treatment effect on OA severity. Pairwise analysis also showed significant differences between Triamcinolone vs. HA (p=0.039) and Triamcinolone vs. PRP (p=0.023), indicating distinct effects of triamcinolone compared with HA and PRP on cartilage and inflammation.

Group 1. Platelet-Rich Plasma (PRP)

Histopathological analysis revealed no cartilage edema or deep ulceration. All specimens showed cartilage erosion (Figure 1A) and superficial/intermediate hypercellularity (Figure 1B). Fissures and superficial ulcers occurred in five animals, and two had complete cartilage loss. Mild basophilia appeared in one case, while osteophytes were present in all.

Isogenous chondrocyte groups averaged one to two per 40x field, with only one specimen showing five or more. Columnar chondrocyte arrangement, suggestive of moderate regeneration, appeared in three animals (Figure 1C).

All animals exhibited villous synovial hypertrophy with synoviocyte hyperplasia, edema, and lymphoplasmacytic infiltration. Synovium and fibrovascular tissue filled trabecular spaces in four cases, whereas two lacked synovial lining. Fibrovascular tissue formation was moderate in all, especially at the cartilage transition.

Inflammation was mild:edema and multinucleated giant cell granulomas were seen in three animals, and non-purulent adjacent myositis in two.

Group 2. Hyaluronic Acid (HA)

Histopathological analysis showed cartilage erosion, fissures, superficial/intermediate hypercellularity, and mid-to-deep involvement in all specimens. Superficial ulcers occurred in five animals, total cartilage loss in three, cartilage flaps in two, and edema with tidemark changes in four. Mild basophilia loss appeared in one case, while osteophytes were present in all.

Isogenous chondrocyte groups averaged 1–2 per 40x field in three animals and ≥5 in one. Columnar arrangement, suggestive of regeneration, was seen in one animal. All displayed mild–moderate villous synovial hypertrophy with synoviocyte hyperplasia (no vacuolization) and lymphoplasmacytic infiltration. Synovial lining partially covered cartilage in four cases and was absent in one (Figure 2).

Fibrovascular tissue formation was moderate in all, mainly in the transition zone. Inflammation was mild in three animals and severe in five, with multinucleated giant cell granuloma. One animal also showed adjacent non-purulent myositis.

Group 3. Chondroitin

Histopathological analysis revealed no edema, basophilia loss, or deep ulceration. All specimens showed cartilage erosion,

hypercellularity across layers, tidemark alterations, and osteophytes. Fissures were found in three animals, superficial ulcers in two, total cartilage loss in two, and cartilage flaps in one.

Isogenous chondrocyte groups were mostly 1–2 per 40x field (Figure 3A), with 3–4 in one specimen. Columnar arrangement, suggesting moderate regeneration, was present in three animals. Four showed mild–moderate villous synovial hypertrophy (Figure 3B) with synoviocyte hyperplasia (no vacuolization) and lymphoplasmacytic infiltration. In one case, the synovial lining partially covered the cartilage.

Fibrovascular tissue formation was moderate in all animals, especially in the transition zone. Inflammation was mild in three and moderate in three.

Group 4. Triamcinolone

Histopathological analysis revealed no edema, fissures, basophilia loss, tidemark changes, or deep ulcerations. All specimens showed superficial/intermediate and mid-to-deep hypercellularity with osteophytes. Superficial ulcers occurred in six animals (Figure 4), total cartilage loss in one, erosion in one, and flaps in another.

Isogenous chondrocyte groups were mainly 3–4 per 40x field (five animals) and 1–2 in three. Columnar arrangement, suggestive of moderate regeneration, was observed in three animals. All showed mild–moderate villous synovial hypertrophy with synoviocyte hyperplasia (no vacuolization) and lymphoplasmacytic infiltration. Partial synovial coverage appeared in two cases, and synovial tissue within trabecular spaces in one.

Fibrovascular tissue formation was moderate in all, especially at the cartilage transition. Inflammation was mild in two animals and moderate in four, with adjacent non-purulent myositis in two.

Group 5. Control

This group (n=6) received only injectable water. Histopathology showed no edema, basophilia loss, or deep ulceration, but all specimens had multi-layer hypercellularity and osteophytes. Cartilage fissures were found in three animals, superficial ulcers in six, total loss in one, erosion in two, and flaps with tidemark alterations in one.

Isogenous chondrocyte groups were ≥5 per 40x field in five animals and 3–4 in three. Columnar arrangement, suggesting moderate regeneration, appeared in three. All exhibited mild–moderate villous synovial hypertrophy with synoviocyte hyperplasia (no vacuolization) and lymphoplasmacytic infiltration. Partial synovial coverage was seen in three cases, with trabecular synovial tissue in one.

Histopathological scores ranged from mild to severe.

Comparison between groups of histopathological findings

The PRP group showed the highest number of columnar chondrocytes, indicating superior cartilage regeneration through chondrocyte maturation and reorganization. Moderate synovial inflammation was observed, with synovial capsule coverage and focal pannus formation.

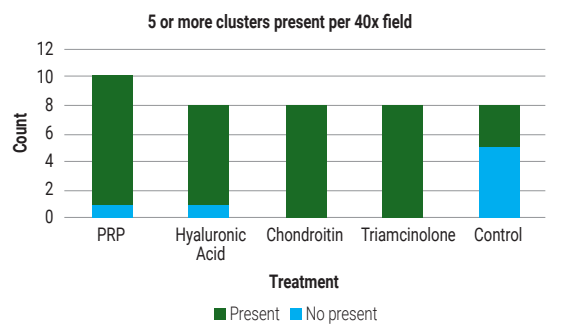
The HA group showed mild cartilage damage, with minimal erosion or ulcers, abundant columnar chondrocytes, and high chondrocyte density, indicating strong regeneration. It also had the lowest synovial and lymphoplasmacytic inflammation, suggesting high regenerative and anti-inflammatory potential

The chondroitin sulfate group showed fewer cartilage flaps and preserved tidemark, indicating tissue maintenance. Along with PRP, it had high columnar chondrocyte replacement and low inflammatory scores.

The triamcinolone group showed the strongest anti-inflammatory effect, with minimal inflammatory infiltration, preserved synovium, no edema, and intact synoviocytes. Cartilage loss was limited to superficial ulcers, with a moderate chondrocyte count, indicating potent anti-inflammatory activity but limited chondroregeneration.

The untreated control group exhibited moderate cartilage lesions and a high inflammatory infiltrate. Although a higher number of chondrocytes per microscopic field was observed, they were not organized in columnar formations, suggesting only mild joint regeneration.

Graph 1: Distribution of groups presenting chondrocyte clusters in histological sections. Source: The authors (2025).



Graph 2: Representation of groups presenting up to 4 chondrocyte clusters in the histopathological assessment. Source: The authors (2025).

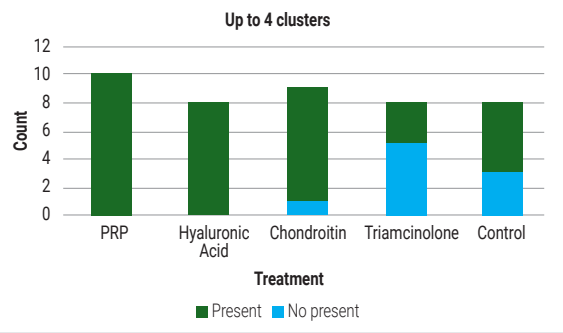
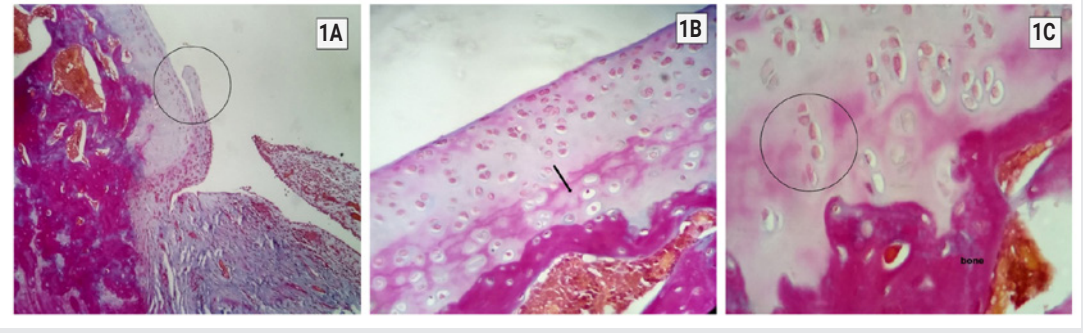
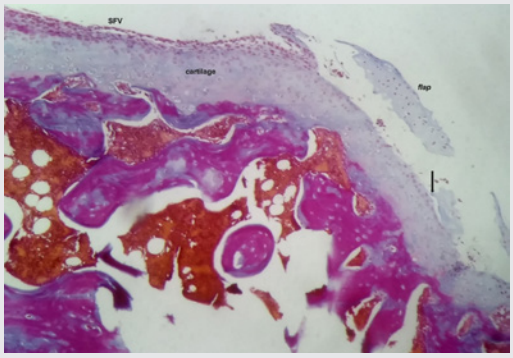


Figure 1: Histological sections of the right femorotibial-patellar joint from group 1 after PRP Application. Source: The authors (2025).



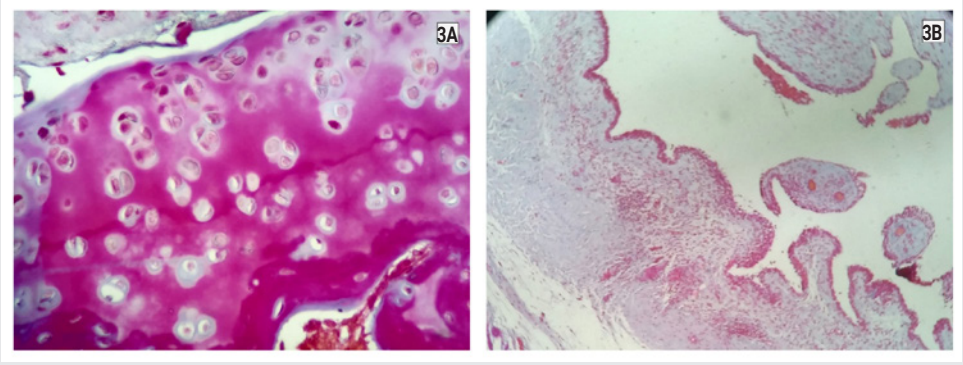
Caption: 1A - Erosion and cartilage fissure, deep wear, and displacement of the cartilaginous margin (circle). Mallory staining, 4x objective. 1B - Moderate hypercellularity and division of the cartilaginous margins (tidemark) (arrow). Mallory staining, 40x objective. 1C - Columnar chondrocytes (circle). Mallory staining, 4x objective.

Figure 2: Reactive synovium and fibrovascular tissue covering cartilage in the right femorotibial-patellar joint. Source: The authors (2025)



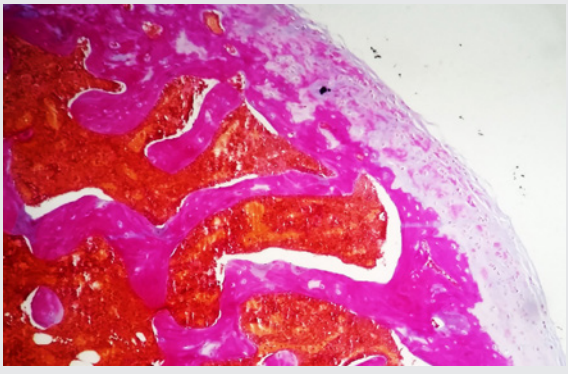
Caption: Mallory's Trichrome staining, 10x objective. SFV: Synovium with fibrovascular tissue infiltration. Arrow: Cartilage fissure and flap formation.

Figure 3: Histological sections of the right femorotibial-patellar joint from group 3 after chondroitin application. Source: The authors (2025)



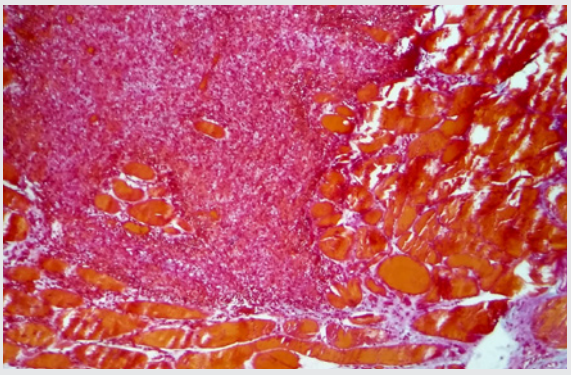
Caption: 3A - Right femorotibial-patellar joint. Isogenous groups of chondrocytes. Mallory staining, 40x objective. 3B - Right femorotibial-patellar joint. Villous hypertrophy of the synovium. Mallory staining, 4x objective.

Figure 4: Superficial ulceration in the right femorotibial-patellar joint. Source: The authors (2025)



Caption: Histological section showing superficial ulcer formation in the right femorotibial-patellar joint. Mallory's Trichrome staining, 10x magnification.

Figure 5: Severe myositis in the right femorotibial-patellar joint. Source: The authors (2025)



Caption: Muscular inflammation. Mallory's Trichrome staining, 4x objective.

DISCUSSION

The histopathological examination of biopsies from the distal epiphysis of the right femur, assessing cartilage, chondrocytes, synovium, and inflammatory cell infiltration, classified all groups as grade 6 according to the Pritzker histopathological classification[14], although differences were observed in the degree of cartilage regeneration, chondroprotection, and inflammation among groups.

The PRP-treated group exhibited the highest number of columnar chondrocytes, indicating superior joint regeneration associated with chondrocyte maturation and cellular reorganization. Moderate synovial inflammation was observed, with the synovial capsule covering the cartilage and focal pannus formation. Similar findings have been reported in experimental murine models[15], including improved articular load distribution, reduced synovial membrane thickness, and less cartilage damage. Taken together, these findings suggest not only pain relief but also a more favorable inflammatory profile, evidenced by a greater presence of anti-inflammatory cells in the PRP-treated group compared with the saline-treated group.

Another aspect discussed in the literature concerns the safety and comparative efficacy of single versus multiple PRP injections. Clinical trials and meta-analyses indicate that multiple injections are superior to a single application; however, administering more than three injections does not appear to provide clinically meaningful additional benefits, suggesting the presence of a therapeutic plateau[16].

The hyaluronic acid (HA) treated group demonstrated mild cartilage lesions, with frequent absence of erosions or superficial ulcers, as well as columnar chondrocyte deposition and high cellular density, suggesting a high regenerative potential. This group also exhibited the lowest levels of synovial and lymphoplasmacytic inflammation, indicating an anti-inflammatory effect, consistent with the proposed role of HA in pain relief among symptomatic patients[17].

Experimental studies have shown that intra-articular injection of saline solution (0.9%) induces changes consistent with osteoarthritis, whereas hyaluronic acid (HA), regardless of molecular weight, exerts a protective effect on articular cartilage[18]. Similarly, different intra-articular HA administration protocols resulted in reduced osteoarthritis in both articular cartilage and the articular disc, with no significant differences related to viscosity or number of injections[19]. These findings are consistent with the PANLAR consensus, which recognizes the clinical benefit of HA across different molecular weights and suggests that product selection should be individualized, without a direct correlation between viscosity and clinical efficacy[17].

However, according to the most recent American College of Rheumatology guideline for osteoarthritis (ACR/AF 2019)[20], intra-articular HA injections are conditionally recommended against for the treatment of knee osteoarthritis. Although not considered a first-line therapy, HA may be an option in selected cases in which NSAIDs, physiotherapy, and corticosteroids fail.

A meta-analysis[21] comparing PRP, HA, and corticosteroids across different follow-up periods demonstrated that PRP consistently achieved the highest WOMAC scores. At three months of follow-up, the efficacy ranking after PRP was placebo, corticosteroids, and HA, whereas at six months the ranking was PRP, HA, corticosteroids, and placebo. Similarly, PRP showed superior results on the visual analog scale (VAS) at three months, followed by corticosteroids, HA, and placebo, in agreement with the findings of the present study, which support the superior performance of PRP.

The chondroitin sulfate-treated group presented fewer cartilage flaps and preservation of the tidemark, indicating maintenance of cartilage tissue. Similar to the PRP group, it exhibited high replacement by columnar chondrocytes and low inflammatory indices, consistent with its chondroprotective and anti-inflammatory effects, which have been attributed to the inhibition of cartilage-degrading enzymes such as hyaluronidase, cathepsin, elastase, collagenase, and neutral metalloproteinases[22].

Cautious recommendations regarding intra-articular biological therapies reflect the heterogeneity and lack of standardization of available products and treatment protocols, affecting PRP, HA, and chondroitin sulfate. In this context, the ACR/AF 201920 conditionally recommends against PRP for knee osteoarthritis due to variability in preparation methods and uncertainty regarding product composition. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)[23] issues a weak recommendation for HA and chondroitin sulfate; the American Academy of Orthopaedic Surgeons (AAOS)[24] provides moderate recommendations for these agents and a limited recommendation for PRP; whereas the PANLAR[17] consensus recognizes PRP as a promising option for pain relief, although still dependent on better standardized studies.

The triamcinolone-treated group demonstrated the most intense anti-inflammatory response, with low cellular infiltration, synovial preservation, absence of edema, and maintenance of synoviocytes. In the articular cartilage, reduced tissue loss was observed, although chondrocyte counts remained moderate, indicating superior anti-inflammatory activity but limited chondroregeneration. This limitation may compromise long-term outcomes and result in the need for repeated applications, reinforcing the role of intra-articular corticosteroids in controlling active inflammatory processes and providing rapid pain relief[17,25].

The OARSI[26] guideline for knee osteoarthritis recommends topical NSAIDs as level 1A therapy, while intra-articular corticosteroids and HA receive conditional recommendations (level 1B). Although effective for acute pain relief, NSAIDs and corticosteroids do not reduce chronic nociceptive pain, and their prolonged use should be approached with caution due to potential adverse effects[26,27].

Based on current evidence, PRP and HA are most appropriately indicated for mild to moderate knee or hip osteoarthritis, providing progressive benefits without altering disease progression. Meta-analyses and clinical trials indicate that combined PRP and HA therapy yields more consistent and sustained improvements in function and stiffness for up to 52 weeks, although with a delayed peak effect. In cases of predominant pain and inflammation, intra-articular corticosteroids remain useful for short-term symptomatic relief and may potentiate HA viscosupplementation, justifying combination therapy, which associates rapid analgesia with more durable functional benefit, including WOMAC score reduction within 2–4 weeks and maintenance of improvement for up to 24–52 weeks, underscoring the importance of individualizing therapeutic decisions[24].

A limitation of this study is the lack of PRP standardization, particularly regarding dosage, sample homogeneity, and centrifugation techniques. Variations in PRP preparation methods alter its blood components and humoral factors[28], highlighting the need for further research to standardize its production. Finally, the untreated control group exhibited moderate cartilage lesions and marked inflammatory infiltrate. Although a higher number of chondrocytes per microscopic field was observed, they were not organized in columnar formations, suggesting only limited joint regeneration.

CONCLUSIONS

This experimental study demonstrates that platelet-rich plasma (PRP) and hyaluronic acid (HA) induce greater regenerative effects on injured articular cartilage than triamcinolone or chondroitin. PRP exhibited a histological pattern characterized by greater chondrocyte proliferation, improved matrix organization, and reduced degeneration, highlighting its potential as a biostimulant in cartilage repair. Although less proliferative, HA contributed to structural preservation and maintenance of articular surface integrity. In contrast, triamcinolone and chondroitin did not promote significant regeneration, exerting mainly anti-inflammatory or maintenance effects.

These findings suggest that biological therapies based on PRP and HA may represent promising alternatives for osteoarthritis management, supporting tissue repair and functional cartilage recovery. However, further studies integrating biomechanical and molecular analyses, as well as long-term evaluations, are required to validate the efficacy and durability of these treatments in preclinical and clinical models.

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