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MINIREVIEWS

Intra-articular interventions in osteoarthritis: Navigating the landscape of hyaluronic acid, mesenchymal stem cells, and platelet-rich plasma

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Abstract

Osteoarthritis (OA) poses a substantial burden on patients, leading to pain, functional decline, and reduced quality of life. While conventional treatments focus on symptom management, disease-modifying interventions are yet to be established. This review explores the efficacy of intra-articular interventions, particularly hyaluronic acid (HA), mesenchymal stem cells (MSCs), and platelet-rich plasma (PRP), in the context of OA management. HA injections, with diverse formulations like Hylan G-F20, sodium hyaluronate, and hyaluronan, present varying outcomes, necessitating a nuanced understanding of their effectiveness and timing. MSC therapy, derived from adipose tissue, umbilical cord, or bone marrow, shows promising results in clinical improvement, with adipose-derived MSCs demonstrating efficacy in maintaining benefits over 6 mo. Conversely, bone-marrow-derived MSCs show limited effectiveness, highlighting the need for source-specific considerations. PRP has emerged as a superior option for long-term pain reduction and quality of life improvement, with leukocyte-poor formulations and a critical platelet count of 10 billion demonstrating optimal results. This comprehensive analysis underscores the potential of intra-articular interventions in OA management, emphasizing the need for personalized and evidence-based approaches to enhance treatment efficacy and patient outcomes.

Key Words: Osteoarthritis, Viscosupplementation; Platelets; Hyaluronic acid; Stem cell

Core tip: Osteoarthritis significantly affects patients by causing pain, functional decline, and reduced quality of life. Traditional treatments mainly manage symptoms, with no disease-modifying interventions established. This review examines intra-articular treatments, including hyaluronic acid (HA), mesenchymal stem cells (MSCs), and platelet-rich plasma (PRP). HA injections show varied outcomes, requiring detailed understanding. MSCs, especially adipose-derived MSCs, demonstrate sustained benefits over 6 mo, while bone-marrow-derived MSCs are less effective. PRP is effective for long-term pain relief and quality of life improvement. Personalized, evidence-based approaches are crucial to enhance treatment efficacy and patient outcomes.

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INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder and the leading cause of disability in older people. Approximately 10% of men and 13% of women over the age of 60 years suffer from OA[1]. These numbers are likely to increase due to the rise in the aging population and obesity rates. It is a degenerative disorder with inflammatory components affecting the entire joint including bone, cartilage, ligaments, fat, and the synovium. The pathophysiology of the disease is complex but can be understood as degradation of articular cartilage and bone remodeling due to the activity of chondrocytes in the cartilage and inflammatory cells in the surrounding tissues. Due to several factors, collagen and proteoglycans are destroyed by enzymes. This exposes the underlying subchondral bone and results in sclerosis. Over time, the joint space is progressively lost. Joint stiffness and pain upon activity lead to functional decline and a decrease in quality of life.

Risk factors for OA include age, female gender, obesity, diabetes, systemic inflammatory diseases, lower limb malalignment (genu valgum and genu varum), trauma, and excessive joint stress[2]. Symptoms of OA include pain and stiffness in joints worsened by activity. Also, pain and stiffness can occur after prolonged rest, known as gelling, and are typically relieved in 30 min. OA can also lead to reduced range of motion in the affected joint, and crepitus. Advanced joint damage may lead to joint deformity: Bouchard nodes (swelling of Proximal interphalangeal joints) or Heberden nodes (swelling of Distal interphalangeal joints) in the hands, and genu varum malalignment in the knees. The diagnosis of OA is based on the clinical features of the disease but can be supported by radiographic findings. Signs on X-rays include marginal osteophytes, subchondral sclerosis, localized joint space narrowing, and cysts formation[3].

Many pharmacological treatments are used to alleviate symptoms of OA[4]. Analgesics like acetaminophen and opioids act as pain relievers. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most used drugs to decrease pain and inflammation, and include aspirin, ibuprofen, diclofenac, naproxen and celecoxib. Other options include the antidepressant duloxetine and the anti-seizure drug pregabalin. These are US Food and Drug Administration (FDA)-approved medications for the treatment of OA pain. Intra-articular pharmacological therapy is another treatment option in the management of OA. Intra-articular drug delivery might be ideal for OA treatment as it delivers the concentrated therapeutic dose throughout the joint capsule[5]. This allows a more direct effect on the joint due to increased bioavailability and less systemic exposure, leading to fewer side effects. It is important to note that intra-articular injections have a strong placebo effect, and some OA symptoms are simply responsive to intra-articular placebo. Corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP) and cell-based therapies like mesenchymal stem cells (MSCs) are examples of intra-articular injections used in the treatment of OA. In this article, we tackle the use of HA, PRP and MSCs. We critically assess the evidence behind their application and evaluate their effectiveness *versus* placebo.

INTRA-ARTICULAR HA INJECTIONS

Viscosupplementation or intra-articular HA (IA-HA) injections have become widely used in clinical practice for knee OA pain relief. Various preparations are commercially available like injections of hyaluronan, sodium hyaluronate and hylan polymers A and B. The FDA has approved the use of HA for pain relief in patients with mild to moderate OA of the knees, who have not responded to conservative nonpharmacological measures and/or analgesics[6]. Contradictory evidence on the use of HA is still present, and recommendations for its clinical application remain inconclusive.

EFFECTIVENESS OF DIFFERENT HA PREPARATIONS

A diverse array of HA derivatives is currently in use for the management of knee OA, but there is a notable lack of consensus regarding the clinical superiority of any specific agent over others.

Hylan G-F20

Hylan G-F20 is a crosslinked HA product derived from rooster comb HA, with a high molecular weight of 6000 kDa. The crosslinking of this formulation enhances its durability by rendering it more resistant to degradation within the knee joint, thereby extending its effectiveness over time. Its high molecular weight imparts elastoviscosity, which contributes to its pain-relieving effects in knee OA[7]. Several studies have investigated the effectiveness of Hylan G-F20 in knee OA.

The LOBRAS study is a 52-week observational study evaluating the effectiveness of a single injection of Hylan G-F20. It found significant improvement ($P \leq 0.025$) in pain relief and function in patients with knee OA[8]. Additionally, total knee replacement was delayed for > 7 years after injection with Hylan G-F20 in 75% of 1863 patients with grade IV knee OA[9]. It is important to note that an increase in knee synovitis was found after repeat injections of Hylan G-F20. The limitation of both these studies was the lack of a control group or blinding. Nonetheless, they offer an outlook on the effectiveness of this type of HA injection in treating the symptoms of knee OA and delaying the need for total knee replacement.

Sodium hyaluronate

Sodium hyaluronate is a salt form of HA. When used as a viscosupplement in treating knee OA, it acts as a lubricant and shock absorber. Supartz (sodium hyalurnate) was the first IA-HA product to receive worldwide approval, with the longest history of global utilization. Large randomized controlled trials have shown that a single treatment cycle of Supartz, comprising 3–5 weekly injections, leads to a significant reduction in pain and a notable improvement in subjective function among patients experiencing mild to moderate symptomatic knee OA compared to a placebo (64% *vs* 31%, $P < 0.001$)[10].

Hyaluronan

Hyaluronan is a high-molecular-weight extracellular matrix polysaccharide and a derivative of HA. Its viscoelastic properties drive its use for knee injection to alleviate the symptoms of OA. Several systematic reviews and meta-analyses have evaluated intra-articular hyaluronan therapy *versus* placebo. Richardson *et al*[11] concluded that the clinical benefits associated with hyaluronan injection were not significant compared to the placebo. This conclusion indicates the inferiority of hyaluronan preparation compared to other HA preparations. However, this hypothesis can only be proven through head-to-head comparison between these different HA derivatives.

After discussing the effectiveness of several HA derivatives in the treatment of OA-related symptoms, it is important to mention that current guidelines are still inconclusive concerning the use of viscosupplemetation for knee OA. Guidelines may change as new data emerges supporting the use of HA injections.

TIMING AND DURATION OF INJECTIONS

The timing and duration of injections are two factors that affect the efficacy of IA-HA. When investigating the best treatment protocol in term of efficacy and injection-related side effects, it was found that single injections of IA-HA did not show significant effectiveness compared to saline injections at 3 and 6 mo follow-up. Two to four injections demonstrated the best results at 3 and 6 mo follow-up. At least five injections conveyed a significant improvement in pain only at 6 mo, and they were associated with a higher risk of injection-related side effects when compared to intra-articular normal saline (NS). This increased risk of side effects was not observed within the one and 2–4 injection subgroups[12].

One study found that pain relief was noted after 3-weekly Hylan G-F20 injections and functional improvement was noted after 8 wk ($P < 0.05$) compared to the placebo group[13]. Two randomized clinical trials found that 5-weekly injections of Hyalgan (sodium hyaluronate) provided sustained pain relief and improvement in function when compared to a placebo on the visual analog scale (VAS) after a 50-foot walking test at week 25[14,15].

The presence of the different subtypes of HA preparations is a variable that should be taken into consideration when analyzing the effectiveness of a specific regimen and treatment-related side effects. These findings suggest that future guidelines should consider the injection regimen for different types of IA-HA treatments, allowing for a more tailored approach to treatment recommendations for knee OA.

SAFETY PROFILE OF IA-HA INJECTIONS

Several studies have assessed the safety profile of IA-HA injections. Side effects were slightly more frequent among patients receiving IA-HA treatment compared to placebo[16]. Side effects included mild transient local reactions such as swelling and pain at the site of injection. IA-HA also showed a small risk of flares and effusion at the injected knee. In comparison with other OA therapies such as acetaminophen or oral NSAIDs, IA-HA was shown to exhibit fewer systemic side effects but more local reactions. In addition, withdrawal due to side effects was less common in patients receiving IA-HA compared to patients receiving acetaminophen or oral NSAIDs. Since OA is primarily a disease of older people, who often have multiple comorbidities, IA-HA offers a treatment option when conventional therapies fail to be tolerated by this group of patients.

Although certain studies have shown that viscosupplementation is effective in relieving arthritis symptoms, it is important to note that there is currently no substantiated evidence supporting its ability to reverse the arthritic process or stimulate cartilage regeneration. The efficacy of viscosupplementation in the treatment of arthritis remains a matter of

ongoing investigation. Continuous studies are being conducted to explore the long-term effects and potential benefits of viscosupplementation in arthritis management.

STEM CELLS

Mesenchymal stem cell (MSC) therapy is a new form of medical treatment where cells are derived from many different sources, with each source possibly having a different efficacy and safety in the treatment of OA. Therefore, it is important to prove the efficacy and safety of SC therapy and to compare and contrast the different sources and explore the different doses and regimens that will provide the patients with the best possible outcomes.

Adipose-tissue-derived MSCs

One type of MSCs that can be used for OA treatment is adipose-tissue-derived MSCs (AD-MSCs). A study was conducted to assess the efficacy and safety of a single intra-articular injection of AD-MSCs for patients with knee OA[17]. Results showed clinical improvement at 6 mo with a significant reduction in the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) and VAS scores ($P < 0.001$) but no severe adverse events. These findings suggest that a single intra-articular AD-MSC injection can maintain clinical improvements for > 6 mo. A second study that used AD-MSCs was conducted in China to assess their efficacy and safety in comparison to HA in patients with symptomatic knee OA[18]. Clinical results for the AD-MSCs and HA groups 6 mo after injection showed significant improvement in the WOMAC score with an improvement rate of 31.65% ($P = 0.0002$) and 20.23% ($P = 0.0001$), respectively. Radiological results 12 mo after injection showed a significant increase in the total knee cartilage volume for the AD-MSCs group ($P = 0.0042$ for the left knee and $P = 0.0307$ for the right knee), while the HA group had a tendency for cartilage to decrease. The outcomes here were reported after a comparatively longer time period of 12 mo, following the administration of two injections at 0 and 3 wk. This suggests that structural cartilage repair is possible when multiple smaller injections are used, and the therapy is given enough time (Table 1).

Table 1 Summary of different treatment modalities

MSCs	PRP	HA
(1) SC therapy utilizes various types of stem cells, such as those derived from adipose tissue, bone marrow, and the umbilical cord	(1) PRP contains elevated platelet concentrations and is used for tissue healing and regeneration, especially in conditions like OA	(1) Various HA derivatives are used for knee OA management, such as Hylan polymers, sodium hyaluronate and hyaluronan
(2) AD-MSC intra-articular injections showed significant clinical and structural knee joint improvement over 6 and 12 mo, respectively	(2) In a laboratory study, PRP and high molecular weight HA were compared in their effects on gene expression and secretion of inflammatory mediators from OA cartilage and synoviocytes	(2) Hylan G-F20, a cross-linked HA product, has demonstrated effectiveness in relieving pain and improving function in knee OA, as well as delaying the need for total knee replacement
(3) UC-MSC intra-articular injections showed significant clinical improvement over 12 mo with multiple injections, however, no structural improvement was observed	(3) PRP injections were found effective even in late-stage knee OA, enhancing pain relief and daily life activities	(3) Sodium hyaluronate, such as Supartz, has demonstrated significant pain reduction and improved function in mild to moderate symptomatic knee OA
(4) BM-MSC intra-articular injections did not show significant clinical or structural improvement	(4) Optimal dosage of PRP with 10 billion platelets showed significant improvements in WOMAC and IKDC scores, along with decreased inflammatory markers like IL-6 and TNF-α	(4) The clinical benefits of hyaluronan injections compared to placebo remain inconclusive, suggesting the need for head-to-head comparisons with other HA preparations
(5) Intra-articular injection of MSCs for OA is a safe treatment that showed no major adverse events	(5) PRP intra-articular injection has promising results for moderate to severe OA symptoms enhancement, regardless of leukocyte richness	(5) Current guidelines regarding viscosupplementation for knee OA are inconclusive and may evolve with emerging data supporting HA injections
	(6) Intraosseous injections of PRP did not provide additional benefits in OA knee treatment compared to intra-articular injections alone	(6) Safety assessments indicate slightly higher local adverse effects with intra-articular HA injections compared to placebo, but fewer systemic side effects than oral NSAIDs or acetaminophen
		(7) Viscosupplementation may offer symptom relief but does not reverse the arthritic process or promote cartilage regeneration, emphasizing the need for ongoing research into its efficacy and long-term effects

PRP: Platelet-rich plasma; OA: Osteoarthritis; MSCs: Mesenchymal stem cells; HA: Hyaluronic acid; UC-MSC: Umbilical cord derived mesenchymal stem cells; BM-MSC: Bone marrow-derived mesenchymal stem cells; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; IKDC: International Knee Documentation Committee; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Umbilical-cord-derived MSCs and bone-marrow-derived MSCs

A second type of MSCs that can be used for the treatment of OA is umbilical-cord-derived MSCs (UC-MSCs). A study to evaluate the safety and efficacy of intra-articular UC-MSC injections in comparison with IA-HA injections in patients with knee OA was conducted[19]. There were two MSC therapy groups, MSC-1 received an injection only at baseline while MSC-2 also received an injection at 6 mo. Clinical results showed the MSC-2 group had significantly lower scores at month 12 in WOMAC (P = 0.05) and VAS (P = 0.03) in comparison to the HA group. The MSC-1 group showed improvement until 9 mo and then its effects decreased and reached the level of the HA group by 12 mo. Radiological outcomes showed no significant improvement in any group. The results of this study suggest that multiple injections of UC-MSCs can cause better long term clinical improvements than a single injection and that UC-MSCs therapy is an efficient treatment choice for OA. However, no structural improvement was shown in both groups regardless of number of injections and time duration, possibly suggesting inferiority to AD-MSCs as treatment for OA. A third type of MSCs that can be used for the treatment of OA, is bone-marrow-derived MSCs (BM-MSCs). In 2016, a study was conducted to assess the safety and efficacy of intra-articular adult human allogeneic BM-MSCs in patients with knee OA[20]. Patients were divided into groups that received different doses (25, 50, 75 or 150 million cells) or placebo and every group received 2 mL HA following the intra-articular injection of BM-MSCs. Clinical results showed a trend of improvement in VAS, ICOAP and WOMAC-OA in all groups with exceptions in the 150 million cells group. However, none of the groups showing that trend had significant improvement. In addition, magnetic resonance imaging showed no difference between the BM-MSCs and placebo groups. The group with the largest concentration (150 million) of BM-MSCs yielded the worst results. These results might yield a significant outcome if the study were repeated with a larger sample size. Nonetheless, the outcome of this study did not support the use of BM-MSCs as opposed to the use of AD-MSCs or UC-MSCs for the treatment of OA. A study comparing the clinical and regenerative outcomes of bone marrow aspirate concentrate (BMAC) augmentation and human umbilical cord blood-derived (hUCB)-MSC injection following high tibial osteotomy (HTO) was conducted[21]. This was a different method of injection than in the previously discussed studies that involved drilling multiple holes that target cartilage defect sites followed with implantation of the SCs with scaffolds. Clinical outcomes were positive for both groups showing significant improvement 33 mo later (P < 0.001). However, the hUCB-MSC group showed significantly better cartilage repair outcomes than the BMAC group (P = 0.04). This different method of implantation following HTO showed a positive regenerative outcome with UC-MSCs, and on top of that, the improved clinical outcomes in both groups remained for as long as 33 mo. This is a long time period in comparison to time periods seen with single intra-articular injections. Whether these improved outcomes are due to the HTO or the targeted injection method, or both, remains unclear. Nevertheless, this suggests the possibility that this invasive method might be able to yield better results. At the same time, the difference in methods of injection makes it difficult to compare the efficacy of UC-MSCs with the previously discussed AD-MSCs as treatment options for OA. Nonetheless, the trend remains the same with BM-MSCs showing less efficacy in repairing cartilage defects sites.

SAFETY OF MSC THERAPY

From all the studies previously discussed, only one[20] had a single severe adverse event where the patient had a related effusion and required hospitalization and observation for an extra day. Adverse events were reported, some of which resolved spontaneously, and others were treated safely. Common adverse events seen throughout the studies include arthralgia, joint effusion, and acute synovitis. Therefore, the information provided suggests that intra-articular injections of MSCs for OA is a safe treatment that can provide patients with significant clinical improvement with little risk for side effects.

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) is an analogous blood product that contains an elevated concentration of platelets in comparison with the baseline platelet concentration. It is used for the biological enhancement of tissue healing and regeneration, and increased levels of growth factors and secretory proteins provided by the concentrated platelets that play a role in enhancing the wound healing process, especially in autoimmune diseases such as OA[22]. In a controlled laboratory study, it aimed to assess the effect of PRP and high molecular weight hyaluron (HA) on the expression of anabolic and catabolic genes and on the secretion of nociceptive and inflammatory mediators from osteoarthritic cartilage and synoviocytes[23]. The synovium and cartilage were harvested from patients undergoing total knee arthroplasty for OA. Both PRP and HA injections resulted in alleviated catabolism, with PRP treatment resulting in reduction of matrix metalloprotein-13 cartilage breaking enzyme and an increase in hyaluronan synthase 2 expression in synoviocytes and an elevation of cartilage synthetic activity compared to HA (P < 0.05) (Table 2).

As for long-term pain reduction, PRP has shown superiority in comparison to HA. This was in a controlled randomized clinical trial that investigated the long-term effect of intra-articular injection of PRP and HA on clinical outcome and quality of life of patients with OA[24]. At 12 mo follow-up, the WOMAC pain score and bodily pain improved in both groups; however, better results were found in the PRP group compared to the HA group (P < 0.001). This study implies that PRP is more efficient than HA for the long-term reduction in symptoms and improving the quality of life of OA patients. Even in late stage OA, a prospective randomized trial assessed the outcomes of PRP injections at 3 and 6 mo *versus* baseline (P < 0.05 and P < 0.03), and implied that a single PRP intra-articular injection is effective for alleviating

Table 2 Comparison between different treatment modalities

MSCs to PRP	PRP to HA	HA to MSCs
(1) Both MSCs and PRP intra-articular injections resulted in pain relief and overall clinical improvement over similar time frames	(1) Both PRP and HA alleviated catabolism, but PRP showed better reduction in cartilage breaking enzymes and increased cartilage synthetic activity	(1) AD-MSC therapy demonstrated superior efficacy over HA injections
(2) Both MSCs and PRP showed significantly better clinical improvement when compared to HA	(2) In a randomized clinical trial, PRP demonstrated superiority over HA in long-term pain reduction and improvement in quality of life for OA patients	(2) AD-MSC-treated patients showed increased knee cartilage volume at 12 mo, indicating potential long-term structural benefits compared to HA
(3) Unlike PRP, AD-MSCs resulted in significant structural improvement, suggesting that they could serve as a more effective long-term treatment option for knee OA	(3) Comparisons between leukocyte-poor PRP and HA showed significant improvement with PRP in WOMAC and IKDC scores at 12 mo	(3) UC-MSC injections, administered in multiple doses, led to superior long-term clinical improvements in knee OA, in comparison to HA injections
		(4) Neither UC-MSC nor HA injections showed structural improvement on radiological outcomes, suggesting potential limitations of both therapies in addressing OA progression
		(5) HA injections offer temporary relief lasting up to several months, compared to UC-MSCs that can last up to 33 mo with invasive methods
		(6) Injections and MSC therapy exhibit favorable safety profiles, with few severe adverse events reported

PRP: Platelet-rich plasma; OA: Osteoarthritis; MSCs: Mesenchymal stem cells; HA: Hyaluronic acid; UC-MSC: Umbilical cord derived mesenchymal stem cells; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; IKDC: International Knee Documentation Committee.

pain and enhancing daily life activities and quality of life in late-stage knee OA[25].

Comparison between the efficacy of leukocyte-poor PRP (LP-PRP) and HA with NS control injections on 87 mild to moderate OA patients' knees, assessed the WOMAC score and International Knee Documentation Committee (IKDC) subjective score[26]. Only the LP-PRP group sustained a significant improvement in both the WOMAC score (21% increase) and IKDC score (40% increase) at 12 mo. As for the optimal dose and concentration of therapeutic PRP, it was shown that receiving PRP (10 billion platelets) led to significant improvements in WOMAC ($P < 0.001$), IKDC scores ($P < 0.001$) and 6-min pain-free walking distance ($P < 0.001$) in comparison to HA group at 1 mo. Also, there was a significant decline in interleukin (IL)-6 and tumor necrosis factor (TNF)-α levels observed in the PRP group ($P < 0.05$) compared to HA at 1 mo. This study demonstrated that a count of 10 billion platelets is crucial in a LP-PRP formulation to have protective effects in moderate knee OA[27].

It is clear from the data that PRP intra-articular injection is an effective treatment with promising results for moderate to severe OA symptom relief. However, whether it is leukocyte rich or poor is solicited in a double-blind randomized trial, comparing the safety and effectiveness of leukocyte-rich PRP (LR-PRP) and LP-PRP for the treatment of OA. Patients had improvements in the mean IKDC subjective score at 12 mo with respect to baseline with improvement from 45.6 to 60.7 in the LR-PRP group as compared with 46.8 to 62.9 in the LP-PRP group ($P = 0.626$). This suggests that there were no clinically significant differences between LR or LP PRP injections seen in the 12-mo follow-up[28]. As for the modality of injection, single intra-articular injection with or without intraosseous injections of PRP in the treatment of OA knee, revealed no additional benefits in introducing the intraosseous injections in these cases[29].

ADVANCES IN ANIMAL STUDIES

Although MSCs have shown efficacy in clinical trials, they have also shown major disadvantages in their regenerative abilities, such as limited *in vitro* proliferative potential, as well as a proliferative capacity that decreases with age. This has led to the development of induced pluripotent stem cells (iPSCs). These cells are an unlimited source of patient-specific pluripotent cells equipped with regenerative capabilities. Despite the significant advantages of human iPSCs (hiPSCs) over other SC types such as MSCs and embryonic SCs, concerns remain regarding their ability to produce true cartilage and their potential tumorigenicity *in vivo*. A comprehensive systematic review on the application of hiPSCs for generating differentiated progeny that can produce high-quality cartilage *in vitro* and regenerate cartilage in osteochondral defects *in vivo* was conducted. The *in vitro* chondrogenesis using hiPSCs was assessed across eight studies. All protocols successfully produced functional chondrocytes capable of generating hyaline cartilage, indicated by high glycosaminoglycan levels, intense safranin O staining, type II collagen immunostaining, and expression of chondrogenic markers such as COL2A1, SOX9, and aggrecan. However, the quality of the cartilage produced varied among studies with the majority being capable of producing high quality cartilage. Eight studies that utilized hiPSC-derived cells, developed through *in vitro* protocols, to treat cartilage defects in animal knee joints were assessed. The studies demonstrated that hiPSC-derived

cells could regenerate hyaline articular cartilage *in vivo*, often producing cartilage of high quality comparable to native tissue. This was confirmed through macroscopic and microscopic analyses, strong type II collagen immunostaining, and intense safranin O staining. One study utilized serial magnetic resonance imaging to monitor postoperative outcomes, noting reduced T2 relaxation times that indicated successful engraftment and matrix formation. Poor cartilage regeneration was only reported by one study. Importantly, none of the four studies investigating tumorigenicity reported the formation of teratomas or tumor-like masses[30].

There have also been other notable advances in research using new techniques in animal studies. New injections such as secretome, an MSC derivate, have been studied and compared to MSCs and HA using sheep models for their efficacy and safety. The results showed a significantly better OA Research Society International OARSI score for the secretome group compared to the HA group ($P = 0.01$). However, although the OARSI score for the secretome group was better than for the MSCs group, there was no significant difference ($P = 0.3$). While there was no significant difference between the secretome and MSC groups, the secretome group showed better OARSI scores, likely due to host rejection, as previous studies have shown some immunogenicity associated with MSCs injections[31].

Other advances such as hUC-MSCs overexpressing miR-140-5p were tested for superior therapeutic effect compared to normal hUC-MSCs intra-articular injection in rat models. Results showed significant differentiation and enhanced articular cartilage self-repair in the miR-140-5p group compared to the normal hUC-MSCs group ($P < 0.01$). However, no significant difference was seen for increased proliferation of hUC-MSCs between the two groups[32].

As for animal studies in HA intra-articular injections, recent research highlights promising outcomes for various innovative therapies. One study demonstrated that a combination of HA, chondroitin sulfate, and glucosamine provided greater chondroprotective effects in rats with early-stage OA compared to HA alone[33]. Another study investigated a novel HA-methotrexate conjugate (DK226), which showed similar antiarthritic effects to oral methotrexate but without the associated side effects[34]. Additionally, nanoparticles made of poly (lactic acid) or poly (lactic-co-glycolic acid) covered with amphiphilic HA are being explored as drug carriers for OA treatment, with studies indicating no toxic effects on synovial membranes and retention in the joint for up to 1 wk[35]. These findings highlight the potential for these advanced formulations to improve OA treatment in clinical settings.

Additionally, in PRP, a meta-analysis in 2024 evaluated the effects of PRP injections on inflammation and histopathological aspects of cartilage and synovium in animal models of OA. The findings indicate that PRP treatment resulted in better outcomes compared to control groups concerning cartilage histology (very low quality evidence; $P = 0.0002$) and synovium histology (very low quality; $P < 0.0001$), as well as reductions in proinflammatory markers such as IL-1 (low quality; $P = 0.002$), IL-6 (very low quality; $P < 0.00001$), and TNF-α (very low quality; $P < 0.00001$). However, PRP treatment did not significantly affect platelet-derived growth factor-A levels (very low quality; $P = 0.81$)[36]. A systematic review examined animal studies in 2021 of intra-articular PRP injections for treating OA. The review synthesized findings on the disease-modifying effects of PRP, comparing it with OA controls or other treatments, different PRP formulations and injection schedules, and combined therapies. Using the SYRCLE tool, bias risk was assessed among 44 articles involving 1251 animals. Results indicated that PRP injections had clinical benefits in 80% and disease-modifying effects in 68% of studies, slowing cartilage damage and reducing synovial inflammation, along with changes in biomarkers. However, optimal PRP formulation, injection timing, and synergistic effects with other therapies remain uncertain, while bias was low in 40%, unclear in 56%, and high in 4% of cases[37].

CONCLUSION

The diverse landscape of intra-articular treatments for OA underscores the need for personalized approaches. While HA, MSCs, and PRP show different modalities and varying degrees of efficacy in addressing symptoms and enhancing the quality of life, ongoing research is essential to refine treatment protocols, establish safety profiles, and determine the most effective formulations to better manage OA and harness regenerative potentials.

FOOTNOTES

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