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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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INTRA-ARTICULAR APPLICATION OF DIFFERENT TYPES OF INJECTIONS IN OSTEOARTHRITIS - LITERATURE REVIEW

Aleksandra Dzwonkowska *[AD] (Corresponding Author, Email address: olszewskaola98@gmail.com)*
Praski Hospital, Aleja Solidarności 67, 03-401 Warsaw, Poland
ORCID ID: 0009-0000-5617-7356

Lidia Jasińska *[LJ]*
National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland
ORCID ID: 0009-0007-2139-0203

Marta Bronikowska *[MB]*
Independent Public Complex of Open Healthcare, Karola Szajnochy 8, 01-637 Warsaw, Poland
ORCID ID: 0009-0006-5800-0929

Karolina Michalczuk *[KM]*
5th Military Clinical Hospital with Polyclinic, Wrocławska ⅓, 30-901 Cracow, Poland
ORCID ID: 0000-0002-4427-9133

Paulina Redel *[PR]*
The University Hospital in Cracow, Mikołaja Kopernika 36, 31-501 Cracow, Poland
ORCID ID: 0009-0005-8770-2383

Kamila Prusinowska *[KP]*
Praski Hospital, Aleja Solidarności 67, 03-401 Warsaw, Poland
ORCID ID: 0009-0002-9512-2934

ABSTRACT

Osteoarthritis (OA) is a complex, multifactorial disease characterized by an imbalance in chondrocyte metabolism, which ultimately leads to the progressive breakdown of articular cartilage. This process results in chronic pain, joint stiffness, and a decline in overall joint function, severely affecting the patient's quality of life. OA is one of the most common causes of disability worldwide and frequently affects weight-bearing joints like the knees, hips, and spine. While there is currently no effective cure for OA, treatment strategies are primarily focused on managing pain, alleviating inflammation, and improving joint mobility. The risk factors for developing OA are diverse and include obesity, advancing age, genetic predisposition, and lifestyle factors, such as physical activity levels and previous joint injuries. Diagnosis of OA is typically made through a combination of clinical assessment and imaging studies, with radiographic features such as joint space narrowing, osteophyte formation, and subchondral sclerosis serving as key indicators. Although a variety of treatments, from non-pharmacological interventions to pharmacological therapies and surgical procedures, are utilized, a definitive, long-term cure for OA remains out of reach. As a result, current research is increasingly focused on potential therapies, such as mesenchymal stem cells, hyaluronic acid, corticosteroids, and platelet-rich plasma, which aim to promote cartilage regeneration and repair without significant side effects. This review examines these treatments, evaluating their mechanisms of action, efficacy, safety, and limitations, and highlights current clinical guidelines, as well as the risks associated with their long-term use.

KEYWORDS

Osteoarthritis, Mesenchymal Stem Cells, Hyaluronic Acid, Corticosteroids, Platelet-Rich Plasma, Intra-Articular Injections

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Introduction.

Osteoarthritis (OA) is a multifactorial disease, the main pathophysiological mechanism is indicated by an imbalance between chondrocyte anabolism and catabolism, manifesting in patients as chronic pain, stiffness and significant limitation of joint mobility, resulting in motor disability and impairment of quality of life. So far no effective treatment for this disease has been invented, primarily due to the limited ability of spontaneous cartilage regeneration [1,2]. Factors that increase the risk of OA include obesity (the strongest factor), metabolic diseases, age, sex, ethnicity, genetics, nutrition, smoking, bone density, and muscle function [3,4]. This disease affects 30.8 million adults in the United States [5]. Diagnosis is usually based on symptoms and clinical examination, but X-ray imaging may help make the final diagnosis. In radiographic images of patients with OA, the most common features include joint space narrowing, osteophyte formation, subchondral sclerosis, and cysts. No causal treatment has been found so far. Current treatment is mainly based on reducing pain and restoring joint function. The available methods include non-pharmacological methods (exercises, knee sleeves, bracing, acupuncture), pharmacological methods (NSAIDs, acetaminophen, duloxetine, opioids, narcotic analgesics), intra-articular injections (steroids, hyaluronic acid, platelet-rich plasma, mesenchymal stem cells), and surgical treatment. Currently, joint arthroplasty is considered the gold standard treatment for OA in patients who have not responded satisfactorily to non-surgical treatment or whose worsening pain reduces their quality of life [4]. This review provides an overview of the mode of action, classification, efficacy, and safety of mesenchymal stem cells, hyaluronic acid, corticosteroids, and platelet-rich plasma in OA. It also examines current clinical guidance and research on their short-term benefits, limitations, and the risks associated with long-term use.

Methods and materials

The review of the literature in the PubMed database, with use of keywords: osteoarthritis, mesenchymal stem cells, hyaluronic acid, corticosteroids, platelet-rich plasma, intra-articular injections. The inclusion criterion was that the articles were published between 1992 and 2024 to ensure the most up-to-date knowledge.

Discussion

Mesenchymal stem cells

Despite significant progress in both surgical and pharmacological treatment, osteoarthritis continues to pose a major challenge, and attaining complete and long-term remission is highly difficult. For this reason, mesenchymal stem cells (MSC) have become the subject of many studies and discussions in the perspective of becoming a promising form of therapy [1]. Is there a chance that MSCs will prove to be the most beneficial and safest alternative among current treatment methods?

MSCs are pluripotent cells capable of self-renewal and differentiation into a variety of specialized cell types, such as neural cells, osteocytes, and chondrocytes. They have been demonstrated to help not only in reducing inflammation, enhancing the production of anti-inflammatory factors, and inhibiting the expression of inflammatory markers but also in supporting the regeneration of chondrocytes and synoviocytes. Additionally, they aid in biological processes like vascularization, cell proliferation, differentiation, and modulation of the inflammatory response [1,7]. These cells can be extracted from various tissues throughout the body, with distinct characteristics and properties based on their tissue origin [6]. At present, three main categories of cells are the subject of extensive investigation: bone marrow mesenchymal stem cells (BMSC), adipose-derived mesenchymal stem cells (ADMSC), and umbilical cord mesenchymal stem cells (UCMSC) [1]. Recent studies indicate that one of the most promising sources of MSCs is the infrapatellar fat pad, which exhibits significantly greater chondrogenic potential compared to cells obtained from subcutaneous fat or bone marrow. However, in clinical practice, the most commonly used source remains bone marrow-derived stromal cells [7]. Hitherto studies present somewhat conflicting results regarding the best source of stem cells. Those derived from adipose tissue demonstrate faster and easier expansion in culture, greater longevity, safety and

efficacy in improving pain compared to those from bone marrow, at the expense of a lower ability to differentiate into osteocartilaginous tissue [2]. Furthermore, in ADMSC therapy, the donor's age has a lesser effect on cell proliferation, which is a significant clinical consideration for elderly patients with osteoporosis. Overall, ADMSCs have a low risk of rejection. The cells are harvested through liposuction, followed by collagenase digestion, centrifugation, and dilution. This process yields a variety of cells, including ASCs, pericytes, fibroblasts, preadipocytes, vascular cells, macrophages, monocytes, and erythrocytes [7]. One of the newer sources of MSCs has become the human umbilical cord (UCMSC), specifically Wharton's jelly mesenchymal stem cells (WJ-MSC). They offer several benefits, including cellular vitality, high efficacy, the ability to prevent cartilage degradation, and the suppression of proinflammatory cytokines (such as TNF-α, IL-1β, TNF-α-stimulated protein-6, IL-1 receptor) [6,8]. These cells have low expression of MHC class I molecules and do not express MHC class II molecules or the stimulatory molecules required for T lymphocyte activation, leading to favorable immune system tolerance. Moreover, it has been shown that a primary culture after only 4 weeks of expansion can already produce a satisfying amount of cells for clinical use. Another key factor is the method of cell collection. At present, most hospitals worldwide consider the umbilical cord as medical waste, and the process of collecting the cells is non-invasive. This allows for easy retrieval of high-quality WJ-MSCs without causing harm to the donors, thus raising no ethical concerns [6]. Another advantage is the fact that intra-articular injections of MSCs are undoubtedly a much less invasive method compared to surgical procedures such as endoprosthetics, which are usually used already in the final stage of the disease, offering pain relief and improvement of joint function. Pharmacological treatment provides effective pain relief and anti-inflammatory effects, but it cannot reverse the damage or promote cell regeneration. Furthermore, it may cause side effects in the gastrointestinal tract, kidneys, and heart, some of which could be life-threatening or result in disability [7]. In recent years, biological drugs have also been gradually introduced, such as interleukin-1 (IL-1) receptor antagonists and adalimumab (TNF antibodies); however, the results have not been satisfactory. Evidence for the effectiveness of physical therapy remains ambiguous [8]. That is why MSC therapy seems so promising. Stem cell transplantation can be applied in both treating early-stage degenerative diseases and in halting disease progression [9]. Their paracrine effects, along with their anti-apoptotic and anti-inflammatory properties, play a crucial role in the regeneration process, even in the early stages of the disease [7]. Another important aspect of stem cell therapy is the choice between autologous and allogenic MSCs. Previous studies have recognized the advantage of the former due to their high regenerative potential. However, it should be noted that the potential of these cells is influenced by many factors, including cardiovascular diseases, which very often occur as comorbidities in elderly patients exposed to degenerative joint disease [9]. The right dose should also be a key element of the therapy. Unfortunately, the results of studies conducted around the world differ. It has not yet been determined whether larger or smaller doses of intra-articular injections would provide better therapeutic effects. Further long-term studies are needed to prove and assess the effectiveness of specific doses [6,7,9]. It seems that stem cells have a promising potential to become a new therapy in the treatment of osteoarthritis [2]. They have many advantages, including: the possibility of use in all joints at the early stages of the disease, they are a minimally invasive method in the form of repeated injections. Nevertheless, it is crucial to develop standardized treatment protocols for this biological therapy, along with an individualized assessment of each patient and their specific condition, taking into account factors such as disease progression, the extent of joint cartilage degeneration, the affected joint, and patient expectations. Today, the gold standard in the treatment of osteoarthritis is still total joint replacement, but perhaps in the near future MSC therapy will become the safest and most effective treatment method for patients [1,7].

Hyaluronic acid

Hyaluronic acid (HA) is a natural key component of the extracellular matrix, which is a polysaccharide from the glycosaminoglycan group [10]. The chemical structure of the components that build HA, i.e. D-glucuronic acid and N-acetyl-D-glucosamine, includes the presence of carboxyl groups making HA hydrophilic and promoting the hydration of the extracellular matrix. HA is negatively charged and has viscous properties, thanks to which it creates a network that provides resistance to compressive forces [10,11]. Pure HA (HMWHA) with a molecule above 1000 kDa occurs naturally in the vitreous body and Wharton's jelly and has anti-inflammatory and immunosuppressive effects [12]. In synovial fluid, it acts as a lubricant, and its interactions with proteoglycans, such as aggrecan, stabilize the structure of the extracellular matrix [11]. It has also been shown that HA has been invited by the CD44 receptor mediating proliferation and proprietary chondrocyte function [13]. The lubrication in the joint and the augmentation of pressure in the synovial cavity

are also feasible due to HA attaching to PRG4 glycoprotein pertaining to synovial fluid, therefore, in OA, when the morphological disorganization of the cartilage occurs, PRG4 levels decrease, which appears as losing durability of the cartilage [14]. Administration of hyaluronic acid injected intra-articularly is called viscosupplementation [15]. Studies conducted on rabbits on lacerated superficial digital flexor tendon and chondral dysfunction show that intra-articular HA injection helps rebuild the mechanical properties of this area and reduces lymphocytic infiltration that diminishes inflammation, which, in the long term, causes a lower chance of tissue fibrosis. It will result in reduced swelling and pressure on the area and in the end reduced patient pain. The research had a control attempt with intra-articular administration of saliva, which did not provide such results [16]. The effectiveness of sodium hyaluronate, which is a representative of HA with a low molecular weight between 500 kDa and 1100 kDa (Hyalgan, Supparts), has shown ambiguous results - only half of the analyzed studies confirmed its advantage over placebo, and the effectiveness was noted after a series of 3 to 5 injections after 23 weeks of use. A randomized study on 369 patients with a cross-linked HA preparation with a mass of up to 2900 kDa (Monovisc) showed that 25% of patients achieved an analgesic effect after a single administration [17]. High molecular weight (6000 kDa) Hylan GF 20 (Synvisc) is a cross-linked substance derived from rooster combs. In a study conducted on a cohort of 1863 patients with stage IV osteoarthritis, intra-articular administration of Hylan GF20 delayed knee replacement surgery by 7 years in 75% of patients. The best effects are seen at 3 and 6 months after the injection. In a study comparing Hyalgan (approximately 600 kDa) to Hylan GF 20 (Synvisc) (6000 kDa) after 6 months, it was shown that Hylan GF 20 significantly reduces long-term pain, while the Hyalgan viscosupplement did not bring such improvement [17]. A single injection of Hylan g-f20 provides a slightly weaker symptomatic effect compared to a single injection of corticosteroids, although corticosteroid injection carries the risk of more serious adverse effects [15]. It has also been noted that cross-linked HA, therefore hydrophobic, provides similar effects to a 3-fold dose of a non-cross-linked preparation, assuming that both preparations have the same mass in kilodaltons. In a placebo-controlled study, cross-linked HA was shown to have a maximum analgesic component for up to 26 weeks after administration [17].

While analyzing the effects of different types of viscosupplements, it is easily visible that the higher the molecular weight and degree of cross-linking of hyaluronic acid, the better its rheological properties [11]. High molecular weight preparations, such as Synvisc, offer fewer

injections, a longer duration of action, and a better analgesic effect compared to lower molecular weight preparations [17]. In one of the meta-analyses, the efficacy of OA treatment was assessed using the VNS (Visual Analog Scale) and WOMAC (Western Ontario and McMaster Universities Arthritis Index) scales, taking into account the potency after 1, 3, 6, and 12 months. The substance with a preferable analgesic effect was PRP (platelet-rich plasma) compared to HA in the 6-month and 12-month follow-up periods. It was assessed that patients had a quicker recovery, a better analgesic effect, and the injection did not increase the risk of side effects [18].

Intra-articular injections of corticosteroids

Corticosteroids act as local anti-inflammatory medications, and their effectiveness in treating osteoarthritis lies in modulating the functions of T and B lymphocytes by interacting with nuclear receptors, which interrupts the inflammatory cascade at various stages [19]. They reduce the activity and production of IL-1, leukotrienes, prostaglandins, and metalloproteinases, which are considered one of the mechanisms for alleviating pain and improving joint mobility in this condition [20]. The most commonly used preparations are methylprednisolone acetate and triamcinolone [21]. Corticosteroids reduce inflammation of the synovial membrane by lowering the levels of aggrecans, collagenases, and pro-inflammatory mononuclear factors and cells. Their action is complex and results in decreased blood flow in the synovial fluid and a reduction in the number of leukocytes, as well as the release of inflammatory mediators. Joint inflammation in knee osteoarthritis is associated with the progression of cartilage damage, which is why corticosteroid injections may slow the progression of the disease. There are two main groups of corticosteroid preparations approved by the FDA for intra-articular injection. They can be divided into one of two groups based on their solubility in water. The first group consists of water-insoluble preparations. These are ester-based preparations (acetonic/acetate). Their characteristic feature is slower release, the formation of microcrystalline particles, and longer retention at the injection site. Such substances include methylprednisolone acetate, betamethasone acetate, triamcinolone acetonide, triamcinolone hexacetonide, and hydrocortisone acetate. The second group – water-soluble preparations – consists of non-ester substances. They differ from the previous group in that they act quickly, do not form aggregates at the injection site, and have a shorter duration of action. Examples

include sodium betamethasone phosphate and sodium dexamethasone phosphate [22,23]. Currently, the most commonly used are triamcinolone acetonide (Kenalog) and non-crystalline methylprednisolone acetate (Depo-Medrol) [21,24]. The recommended dose of these medications is 40 mg, and the interval between subsequent injections should be at least three months. The advantage in terms of frequency of use lies with triamcinolone acetonide due to its retention time in plasma and consequently its therapeutic effect [21]. The total absorption of triamcinolone acetonide (TA) from the joint lasts about three weeks, and its presence in the plasma can be detected after six weeks. In contrast, the extended-release triamcinolone acetonide (FX006) can maintain the concentration of the drug in the joint within a specific range for an extended period, with a mean residence time (MRT) of up to 19 days. Another advantage of this medication is its effect on glucose metabolism. It may be a good choice for diabetics. Due to its lower solubility in water, it can alleviate pain associated with degenerative disease with minimal impact on glucose levels in the body. Methylprednisolone acetate can significantly relieve pain in patients in the early stages of the disease. Studies show that the effectiveness of the injectable MPA reaches its peak after two weeks, and its effects can last up to 24 weeks [24]. Compared to the preparations mentioned above, the MRT of water-soluble formulations is relatively shorter. They are preferred for superficial injections because they are less likely to lead to the atrophy of subcutaneous fat tissue or skin depigmentation [21].

Based on the review of the guidelines "Recommendations for the Treatment of Osteoarthritis of the Hip and Knee," all guidelines recommend the use of corticosteroids in intra-articular injections for the knee joint. However, the use of corticosteroids for hip joint injections was inconsistent, with three out of four guidelines recommending them, one of which strongly advocated for their use [25]. Nevertheless, the scientific evidence regarding the effectiveness of intra-articular steroid injections is ambiguous and controversial. A recent Cochrane review analyzed 27 low-quality RCTs with high heterogeneity, involving a total of 1,767 patients. The results showed that one month after the administration of intra-articular corticosteroids (I-CS), the improvement in pain compared to placebo was only 1 on the VAS scale. After 13 weeks, the therapeutic benefits were even smaller, and the effect completely disappeared after 26 weeks. The review also utilized the WOMAC scale to assess functional improvement following I-CS injections. Moderate improvement was observed within 1-2 weeks. However, this effect diminished after 4-6 weeks and disappeared after 13 weeks [19]. Corticosteroid injections have no greater effect on pain than placebo after three months and may be less effective than physical therapy after one year [20]. According to researchers, corticosteroid injections are most effective for short-term treatment of joint pain and should not be administered to symptomatic joints more than four times a year due to the increased risk of joint cartilage destruction [21,22,24,26]. According to retrospective literature studies, most patients with osteoarthritis experienced mild to moderate functional improvement within 6 weeks after corticosteroid injection; however, after this period, patients' symptoms did not show significant improvement [24]. Available literature indicates that delivery injections of corticosteroids appear to be generally safe, with an incidence of adverse effects comparable to placebo, primarily involving mild and self-limiting side effects [27]. However, it is important to remember the possible complications associated with prolonged use. The most commonly reported adverse effects were pain at the injection site and exacerbation after injection [22,27]. Although pain at the injection site is often mentioned as an adverse effect, few studies provide its exact frequency, which appears to range from 1.3% to 6.8% of procedures. Exacerbation after injection refers to a local increase in inflammation and pain that develops within a few hours after the injection and can last from two to three days. These were reported in 2% to 25% of cases of intra-articular glucocorticoid injections [27]. Among other adverse effects, subcutaneous atrophy, skin depigmentation, and soft tissue calcifications were noted. Among the systemic adverse effects of intra-articular corticosteroid injections, facial flushing (related to a histamine-mediated reaction), hyperglycemia in diabetic patients, adrenal suppression, and menstrual disorders were mentioned [22]. One of the more serious side effects is the impact of injections on articular cartilage, where they alter the metabolism of the cartilage matrix, and the mechanical properties of articular cartilage, and lead to chondrotoxicity, which may accelerate the progression of osteoarthritis [22,24]. Recent studies have shown a causal relationship between high doses and prolonged use of corticosteroids and the development of chondrotoxicity. Therefore, for short-term symptom relief, intra-articular corticosteroids should not be injected into symptomatic joints more than four times a year [24]. Furthermore, prolonged use of corticosteroids leads to osteoporosis due to bone catabolism and limited bone formation resulting from osteoblast dysfunction and apoptosis [22].

Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is the processed autologous peripheral blood with a platelet concentration above the baseline. In addition, PRP contains the complete complement of clotting factors and is enriched with growth factors (GFs), chemokines, cytokines, and other plasma proteins. The process of obtaining PRP involves differential centrifugation of the small volume of the patient's blood, which separates blood components according to their density. Although no preferred method of PRP preparation has been established, two preparation techniques can be distinguished: open, in which the product is in contact with the environment, and closed, which is preferred due to the lack of contact between the product and the environment [28]. The platelet concentration in PRP is 1 407,640+/-320,100/l and 5 times higher than peripheral blood [29]. The use of PRP in the treatment of tissue damage leads to the achievement of supraphysiological concentrations of GFs. They are responsible for angiogenesis, proliferation, and maturation of chondrocytes, recruitment of stem cells, and inhibition of macrophages and lymphocytes. In addition, PRP creates fibrin gel, which is a scaffold for GFs, allowing for the controlled release of GFs in the intended area. This leads to stimulation of the healing cascade and accelerates the repair of damaged cartilage [30]. A summary of meta-analyses performed by Pu Chen and others demonstrated that, in short-term follow-up, platelet-rich plasma (PRP) intra-articular injection in knee osteoarthritis is more effective in decreasing pain and improving joint function than hyaluronic acid and placebo. The risk of additional effects was similar in PRP injection, HA injection, and placebo. Moreover, Pu Chen noted that in the meta-analyses published over 3 years, only one indicated similar efficacy of HA and PRP, while the others emphasized PRP's superiority in knee osteoarthritis [31]. The most recent systematic review and network meta-analysis, including 3104 participants, concluded that PRP and PRP + HA effectively relieved pain and improved function at 3, 6, and 12 months of follow-up. Moreover, PRP did not increase the risk of adverse events compared to placebo [26]. The specific amount and frequency of PRP doses in treating knee osteoarthritis are not specified in the literature. In clinical trials, 3 PRP injections at 1 week intervals are commonly used in knee osteoarthritis (KOA), whereas in ankle osteoarthritis, it is 2 injections [32,33,34]. The study by Bansal et.al. determined PRP with absolute counts of 10 billion platelets in a volume of 8 ml as an effective treatment of knee osteoarthritis, which leads to significant chondroprotection and relief of symptoms [35]. The biggest complication with using PRP is the lack of clear regulations regarding the formulation and composition of PRP intended for injection [36]. Among the available PRP preparations, we can distinguish leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP). Romandini et al. in a double-blind randomized controlled trial revealed that there is no difference in safety and efficacy of the leukocyte concentration in PRP [37]. A similar solution was reached by Johal et al., who found in a systematic review and meta-analysis that leukocyte concentration, platelet concentration, or the use of an exogenous activator did not significantly influence the treatment effect [38]. The efficacy of PRP in hip osteoarthritis has also been proven in Randomized Clinical Trials. Intra-articular application of PRP in hip osteoarthritis resulted in pain reduction and functional improvement. Furthermore, the addition of HA to PRP was not associated with a better therapeutic effect [39]. In the case of ankle osteoarthritis, the effectiveness of PRP has not been proven in a randomized controlled trial [36].

Conclusions

Various preparations compete for the title of the best specimen administered intra-articularly in the treatment of OA; however, at the same time, it is not possible to clearly determine which one will be the most effective. MCSs appear to be a promising approach for treating osteoarthritis, as they have the ability to regenerate cartilage, reduce inflammation, and promote biological processes within the joint. MSCs can be sourced from various tissues, with umbilical cord-derived cells being particularly noteworthy for their strong regenerative capabilities and immune tolerance. MSC therapy offers a less invasive option compared to surgical procedures and is considered safer than pharmacological treatments, which have limited tissue regeneration potential. Although MSCs may prove effective in clinical practice, additional studies are required to determine the best therapeutic protocols, dosages, and to confirm their long-term efficacy or any possible side effects. Currently, joint replacement remains the standard treatment, but MSC therapy may become a more effective alternative in the future. Studies indicate that HA supports cartilage protection by limiting chondrocyte apoptosis, which may translate into pain relief and restoration of basic morphological parameters of the joint, and thus improvement of the patient's quality of life. In turn, other analyses suggest that PRP brings better results in short-term improvement of joint function and also provides long-term pain relief compared to HA. The rheological properties of HA are greater the higher the molecular weight and degree of cross-linking of the acid formulation. Stabilized hyaluronic acid, i.e., one that additionally has cross-links in

its structure, causes the formation of a 3D matrix, which in effect slows down its degradation, prolonging its effect. It can therefore be concluded that intra-articular HA viscosupplementation is effective, but the analgesic effect is comparable to the administration of NSAIDs. Corticosteroids play a significant role in the management of osteoarthritis by reducing inflammation and providing short-term pain relief. Their mechanisms of action, including modulation of inflammatory mediators and suppression of synovial membrane activity, make them a widely used option for intra-articular injections. However, while corticosteroids offer notable benefits in alleviating symptoms, their long-term effectiveness remains controversial. Evidence suggests that their therapeutic effects diminish over time, and repeated use may contribute to cartilage damage and other systemic adverse effects. Given these concerns, corticosteroid injections should be administered cautiously, adhering to recommended dosing intervals to minimize risks. Ultimately, while they remain a valuable tool for managing osteoarthritis, their use should be balanced with other treatment modalities, including physical therapy and lifestyle modifications, to ensure optimal patient outcomes. PRP seemed to be an ideal preparation for the treatment of OA due to its autologous origin and its influence on the healing cascade, resulting in the repair of damaged cartilage. Despite numerous studies confirming the efficacy and superiority over HA of PRP in relieving pain and improving function in KOA, no clear guidelines can be created for using PRP in osteoarthritis. This is due to methodological errors in the studies conducted and the low level of evidence. Therefore, further large randomized trials are required to confirm the efficacy of PRP and to determine the frequency of administration, formulation, and composition of PRP intended for injection. The choice of the most accurate method should therefore depend on the patient's individual symptoms and realistic therapeutic expectations, as well as the patient's comorbidities, financial resources, and the availability of a specific treatment method.

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