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The Use of Platelet-Rich Plasma and Hyaluronic Acid in the Treatment of Knee Osteoarthritis – A Review of Current Clinical Evidence

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Abstract

Introduction:

Knee osteoarthritis (KOA) is one of the most common causes of chronic pain and disability worldwide. With an aging population, the number of patients requiring effective, yet safe treatment methods are increasing. In recent years, growing attention has been given to therapies involving hyaluronic acid (HA) and platelet-rich plasma (PRP), both as monotherapies as well as combination therapy.

Aim of the Study:

The aim of this study is to compare the efficacy and safety of HA and PRP in the treatment of KOA, as well as to evaluate the therapeutic potential of combined PRP+HA therapy.

Materials and Methods:

A review of current literature was conducted, focusing on the pathophysiology of knee osteoarthritis (KOA), mechanisms of action of hyaluronic acid (HA) and platelet-rich plasma (PRP), as well as

clinical trials and meta-analyses comparing the effectiveness and adverse effects of each therapy. The source materials were primarily obtained from reputable scientific databases such as PubMed and Google Scholar.

Results:

PRP demonstrates superiority over HA in terms of long-term pain reduction and improved knee joint function, owing to its regenerative and anti-inflammatory properties. HA, particularly in the form of high molecular weight HA (HMW HA), improves the rheological properties of synovial fluid and reduces joint friction. Combined PRP+HA therapy proved to be more clinically effective than either treatment alone, also showing a lower incidence of adverse effects.

Conclusions:

Combined PRP and HA therapy may represent the most beneficial treatment strategy for KOA, especially in moderate to advanced stages of the disease. However, further well-designed clinical studies with long-term follow-up are needed to confirm its superiority over monotherapy

Keywords:

knee osteoarthritis, hyaluronic acid, platelet-rich plasma, combination therapy, PRP, HA, joint pain treatment, cartilage regeneration, intra-articular injections, non-surgical treatment of KOA

Introduction

Osteoarthritis is one of the most common diseases; it is approximated that 250 million patients suffer from OA [1], and it is the leading cause of disability in the US and worldwide [2]. It was reported that knee osteoarthritis (KOA) in the USA reached nearly 27 million cases, and the number is constantly growing due to the aging population. KOA is a chronic and degenerative cartilage illness characterized by subchondral bone hyperplasia, cartilage exfoliation, and cartilage degradation. It mostly affects

older people, especially women [3]. In addition to pain, stiffness, edema, joint deformity, and functional impotence, the disorder can also cause muscular atrophy at an advanced stage, lowering the quality of life for patients.

Among common therapeutic approaches used in rehabilitating OA patients, one can distinguish between Manual Therapy (MT), electrotherapy, and therapeutic exercise. Manual Therapy is a practical physiotherapy treatment that can decrease a patient's level of pain and improve their functionality [3]. Currently, there are no established treatments to deviate KOA development. However, patients frequently undergo several treatments to stop the progression. Current treatments focus on symptom remission. Both pharmacological and non-pharmacological methods are used to treat nonsurgical therapy. Suggested non-pharmacological treatments are diet and exercise, which are frequently not followed [4].

Oral glucosamine, chondroitin, acetaminophen, celecoxib, and glucosamine constitute the mainstay of pharmacological therapy for KOA. Nevertheless, adverse effects are frequently associated with the use of analgesics and NSAIDs [4]. According to current reports, intra-articular injection is a safe, efficient, minimally invasive treatment for this condition. Other non-surgical therapy options for patients with KOA include intra-articular injections of palate-rich plasma PRP and hyaluronic acid (HA) [4].

Pathophysiology of knee osteoarthritis

Osteoarthritis (OA) of the knee is a chronic, progressive condition that affects all components of the joint: cartilage, synovial membrane, subchondral bone, ligaments, muscles, and the surrounding adipose tissue. Modern understanding of OA pathophysiology considers not only the mechanical wear of joint structures but also the activation of low-grade inflammatory and immunological processes [5,7].

Changes in articular cartilage include the loss of proteoglycans and collagen, leading to thinning, decreased elasticity, and eventual destruction. This process is driven by pro-inflammatory cytokines present in the synovial fluid, such as IL-1β, IL-6, and TNF-α, which stimulate the production of matrix-degrading enzymes, particularly matrix metalloproteinases (MMPs) [5,7]. Cartilage itself is not innervated or vascularized, therefore early pain symptoms are more likely a result of changes in the surrounding joint structures [7].

The synovial membrane in OA exhibits characteristics of chronic, focal inflammation (synovitis), with a predominant presence of macrophages, unlike rheumatoid arthritis, where T lymphocytes are more prevalent [5]. In the knee joint, inflammatory changes in the synovial membrane are usually localized in the suprapatellar pouch, and the severity of inflammation may correlate with disease progression [5,7]. Moreover, studies show a higher accumulation of macrophages in the synovial membrane of the

knee compared to the hip joint, suggesting differences in the molecular mechanisms between these OA locations [6].

Synovial fluid in OA contains a range of inflammatory mediators, including cytokines (IL-1β, IL-6, IL-17, IL-18, TNF-α), chemokines (MCP-1, IP-10), prostaglandins (PGE2), leukotrienes, acute-phase proteins (CRP), and complement components [7]. These inflammatory factors not only contribute to cartilage destruction but also, activate immune cells and lead to remodeling of the subchondral bone, resulting in osteophyte formation and bone sclerosis [5,7].

In the context of immunological processes, the innate immune system, particularly macrophages, plays a crucial role. Fragments of degraded extracellular matrix (known as DAMPs) activate innate immunity receptors, leading to a chronic inflammatory response, initially protective but ultimately destructive in the long term [7].

OA also shows disruptions in the activity of growth factors, such as TGF-β, BMP-2, and FGF-18. While these factors typically promote tissue regeneration under physiological conditions, in OA, they can drive osteophyte formation and fibrosis [5,7]. The imbalance between degradative and regenerative mechanisms is one of the key features of OA.

Hyaluronic Acid

Hyaluronic acid (HA) is a long, negatively charged, and unbranched polysaccharide composed of repeating disaccharides of D-glucuronic and N-acetyl-D-glucosamine, with molecular weight (MW) reaching up to 2×10^7 Da [8]. It is synthesized by fibroblast-like cells, known as synoviocytes type B. There exist three isoforms of hyaluronan synthases in humans, namely HAS1, HAS2, and HAS3. They are integral membrane proteins. HAS1 and HAS2 are responsible for the polymerization of HA chains up to 2000 kDa, whereas HAS3 polymerizes shorter HA chains of the length of 200–300 kDa [9].

HA is classified based on its molecular weight into low molecular weight HA (LMW, <500 kDa), which is characterized by high bioavailability and the ability to penetrate tissues but also exhibits pro-inflammatory properties—activating immune cells, including macrophages. As a consequence, its use in OA is limited, although it may be useful in the early phases of regeneration. Medium molecular weight HA (MMW, 800–2000 kDa) exhibits moderate structural surface protection and anti-inflammatory properties. Preparations containing MMW HA improve the rheological properties of synovial fluid and support cartilage repair processes. High molecular weight HA (HMW, >2000 kDa) is considered the most effective in OA therapy. It is characterized by high viscosity, strong anti-inflammatory effects, and the ability to form a protective layer on the cartilage surface. Additionally, HMW HA reduces the activity of metalloproteinases and inflammatory cytokines, alleviates pain, and improves joint biomechanics. Numerous studies suggest that HMW HA-based preparations have a longer duration of action and significantly improve patient comfort [10].

HA is commonly found in both synovial fluid and articular cartilage. For many years, it was

considered the main molecule responsible for cartilage lubrication. However, its ability to provide boundary lubrication is limited, as confirmed by experimental studies using the surface forces balance (SFB) technique [11]. Recent studies by Zhu et al. [12] demonstrated that friction between two HA layers attached to surfaces was significantly reduced (from $\mu \approx 0.3$ to $\mu \approx 0.001$) after the addition of small unilamellar vesicles (SUVs) composed of phosphatidylcholine (PC) lipids.

In the context of bio surface lubrication, it is known that PC lipids interact with HA molecules [13]. Seror et al. [14] proposed a boundary lubrication mechanism of articular cartilage based on their research, which showed that PC lipids in the gel phase form complexes with HA molecules bound to the surface, providing strong boundary lubrication. According to this model, PC lipids, HA, and lubricin interact synergistically. Lubricin binds HA on the cartilage surface, while PC lipids form complexes with HA molecules, exposing highly hydrated phosphocholine groups in the sliding plane between opposing cartilage surfaces, which ensures an exceptionally low friction coefficient due to hydration lubrication. In addition to lipid bilayers and monolayers, HA molecules can also be bound with multilayer lipid structures or intact liposomes.

The mechanism of action of intra-articularly administered HA (I-HA) is not fully understood. However, it is believed that it may reduce joint friction, improve elasticity, and support shock absorption, translating into better joint protection. Moreover, some reports suggest that I-HA may limit inflammatory processes by inhibiting phagocytosis and reduce pain perception by blocking pain receptors. Some authors also suggest that this form of therapy may be particularly beneficial in patients with the so-called "dry" type of osteoarthritis [15].

To assess the effectiveness of hyaluronic acid, the study by Gigis I et al. [16] can be cited. The study included patients diagnosed with knee OA who were randomly assigned to two groups: one receiving injections of a high molecular weight HA (HMW HA) preparation and the other a low molecular weight HA (LMW HA) preparation. Both groups were evaluated for pain reduction and joint function improvement using the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Results showed that both groups experienced significant improvement in pain relief and joint function following a series of injections. Specifically, the HMW HA group showed greater improvement in pain reduction, although differences between groups were minimal, and joint function improvement was similar. Patients receiving HMW HA reported noticeable improvement in daily functioning, although the differences between groups were not statistically significant regarding joint function. Both preparations were well-tolerated, and adverse effects were rare.

Discussion of the results indicates that both high and low molecular weight HA preparations can be effective treatments for knee OA. Although the HMW HA preparation demonstrated greater efficacy in pain reduction, both had a similar impact on joint function improvement. This may suggest that

different HA preparations act on different mechanisms within the joint, and the higher molecular weight of HMW HA may more effectively improve synovial fluid viscosity and reduce friction between joint surfaces. Conversely, LMW HA preparations may better penetrate tissues, influencing cartilage repair processes. The conclusions of this study indicate that high molecular weight hyaluronic acid preparations may be more effective in reducing pain and improving joint function compared to low molecular weight preparations. Therefore, HMW HA may be a preferred therapeutic option in knee OA treatment, particularly in patients with significant pain symptoms. Nevertheless, further studies are needed to better understand the mechanisms of action and long-term effectiveness of both preparations in OA treatment.

The use of hyaluronic acid in the treatment of osteoarthritis might be associated with certain side effects. The most reported include headache, diarrhea, skin itching, stomach discomfort, knee swelling, nausea, vomiting, loss of appetite, and localized skin swelling. More serious adverse reactions have also been identified, such as difficulty swallowing, coughing, fever, redness and swelling at the injection site, chest tightness, shortness of breath, wheezing, swelling of the eyelids and lips, rash, and hives. However, it is important to note that both mild and severe side effects are quite rare, affecting less than 5% of patients. Importantly, hyaluronic acid does not worsen the condition of the joint prior to treatment. For this reason, it is considered a safe and effective therapeutic option for individuals with osteoarthritis [17].

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a regenerative medicine product that is becoming increasingly used in therapeutic settings. Compared to in vivo plasma, PRP is autologous plasma that has been processed to have a higher concentration of platelets. Although the concentration of platelets in PRP is not standardized, it is generally believed to be between two and eight times that of autologous serum [15]. Literature suggests that lower concentrations of platelets (< 2× baseline platelet count) do not contribute to faster wound healing [18]. Similarly, no further improvement in treatment outcomes has been observed with significantly higher concentrations of platelets in PRP preparations [19].

PRP preparation techniques may vary; however, the general process involves venesection of a small amount of peripheral blood followed by centrifugation to concentrate the platelets in plasma. Growth factors are released when platelets degranulate, with thrombin, cytokines, and other growth factors present in the plasma. The effects of the single- and double-spinning methods on platelet separation in centrifugation remain a subject of debate [20].

Upon injection into the knee, PRP exerts its effects through the release of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and insulin-like growth factor-1 (IGF-1), which stimulate tissue regeneration and repair processes. This mechanism

involves chondrocyte proliferation, extracellular matrix synthesis, and the promotion of angiogenesis, all of which contribute to cartilage restoration. Additionally, PRP exhibits anti-inflammatory properties by modulating pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which may slow the progression of osteoarthritis and alleviate pain symptoms in the knee joint [21].

Superiority of PRP treatment over HA treatment in KOA

A randomized clinical trial by Seyed Ahmad Raeissadat et al. titled *The Comparison Effects of Intra-Articular Injection of Platelet-Rich Plasma (PRP), Plasma Rich in Growth Factors (PRGF), Hyaluronic Acid (HA), and Ozone in Knee Osteoarthritis: A One-Year Randomized Clinical Trial* included 354 patients who underwent four different injection treatments: PRP (2 doses with a 3-week interval), hyaluronic acid (3 doses weekly), ozone (3 doses weekly), and PRGF (2 doses with a 3-week interval). The effectiveness of these therapies was assessed using three scales: the Visual Analogue Scale (VAS), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Lequesne Algofunctional Index. The results showed that PRP was highly effective in reducing pain and improving knee joint function in patients with osteoarthritis (OA). The scales of WOMAC, Lequesne, and VAS indicated that PRP led to noticeable improvements within two months post-injection, with patients experiencing significant pain reduction and increased joint mobility compared to baseline values.

Over a six-month period, PRP remained more effective than ozone therapy, which started to lose its effects after 4–6 months. During this period, the efficacy of PRP was comparable to hyaluronic acid (HA) and PRGF. However, long-term analysis indicated a superiority of PRP over HA and ozone therapy. After 12 months, PRP showed significantly better results in the assessed scales compared to these other methods. Only PRP and PRGF maintained long-term effectiveness, suggesting their regenerative potential that goes beyond symptomatic relief.

The mechanism of action of PRP involves not only pain relief but also a positive influence on the joint microenvironment. Stimulation of chondrogenesis, modulation of inflammatory processes, and cartilage tissue regeneration may explain its superiority over HA, which degrades in inflammatory conditions, and ozone therapy, whose effects are short-lived [22].

Comparison of Adverse Events in Platelet-Rich Plasma (PRP) and Hyaluronic Acid (HA) Therapies – in Monotherapy and Combination Therapy

In the context of treating knee osteoarthritis (KOA), increasing emphasis is placed not only on therapeutic efficacy but also on the safety of the applied treatment methods. In a systematic review and meta-analysis conducted by Zhang et al. [23], the incidence of adverse events associated with PRP, HA, and combination therapy with PRP + HA was assessed.

The analysis revealed that therapy using PRP alone, although generally considered safe, was associated with a higher incidence of mild adverse events such as pain or swelling at the injection site. However, the meta-analysis, which included 859 patients across 9 studies, showed that the combination of PRP with HA resulted in a significantly lower rate of adverse events compared to PRP monotherapy. The risk of adverse effects was reduced by as much as 47% (RR = 0.53; 95% CI: 0.35–0.81; p = 0.003).

Although the analyzed data did not include a direct comparison of HA as monotherapy, previous reports indicate that hyaluronic acid also has a favorable safety profile [17]. Nevertheless, it was the use of HA in combination with PRP that resulted in the lowest incidence of adverse events among the evaluated therapies.

In summary, the combined PRP + HA therapy, although not showing significantly greater clinical efficacy compared to PRP alone (therapeutic effects did not exceed Minimal Clinically Important Difference – MCID threshold), was found to be notably safer. Therefore, the combination of PRP and HA may be considered the preferred treatment option in KOA patients where minimizing the risk of adverse events is a key consideration.

Potential for Combining Both Therapies

In recent years, there has been growing interest in the potential of combining platelet-rich plasma (PRP) and hyaluronic acid (HA) for the treatment of knee osteoarthritis (KOA). While both therapies are widely used individually, their combination may offer additional clinical benefits for patients.

Numerous studies suggest that PRP+HA combination therapy may be more effective than using either method alone. A meta-analysis involving 11 randomized controlled trials with a total of 1023 participants demonstrated significant clinical and statistical advantages of the combined therapy. The PRP+HA group showed greater pain reduction (VAS), improved joint function (WOMAC, IKDC), and a lower incidence of adverse events compared to PRP alone [24].

Specifically:

- The mean difference in VAS scores was -4.27 (95% CI: -4.96 to -3.58; $p<0.001$), indicating significant pain relief [24],
- Improvement in WOMAC scores was MD -1.77 (95% CI: -2.20 to -1.34; $p<0.001$) [24],
- The risk of adverse events was significantly lower in the PRP+HA group (RR 0.41; $p<0.001$), suggesting a high safety profile for the combination therapy [24].

Similar conclusions were drawn in earlier studies. Zhao et al. confirmed that PRP+HA therapy was more effective in alleviating KOA symptoms than PRP alone, especially within the first 6 months after treatment [25]. Interestingly, the authors noted that, while the differences between groups were

statistically significant, not all surpassed the threshold of minimal clinically important difference (MCID), which should be considered when interpreting the data [25].

Zhang et al. found that the positive effects of PRP+HA therapy persisted for up to 12 months, suggesting durability of the combined treatment's efficacy [23]. These findings reflect a broader trend in exploring therapeutic synergy—combining the regenerative properties of PRP with the protective, anti-inflammatory effects of HA may lead to superior clinical outcomes [23,24].

It is also worth noting that, Du et al. found PRP alone to be more effective than HA alone in reducing pain and improving function, indicating that PRP should serve as the primary treatment, with HA potentially acting as a supportive agent [24].

In summary, current literature suggests that combining PRP and HA is not only safe but also more effective in treating KOA than either therapy alone. The combination appears particularly beneficial for patients with moderate to advanced stages of the disease. However, due to heterogeneity among studies and differences in treatment protocols, further long-term studies with standardized outcome measures are needed.

Conclusions

Knee osteoarthritis (KOA) is a chronic, progressive degenerative joint disease, with treatment primarily focused on symptom relief due to the lack of effective methods to slow its progression. In recent years, therapies using hyaluronic acid (HA) and platelet-rich plasma (PRP) have gained increasing popularity, both as monotherapies and in combination therapy.

Hyaluronic acid, particularly in its high molecular weight form (HMW HA), exhibits anti-inflammatory properties, reduces joint friction, improves synovial fluid viscosity, and alleviates pain. On the other hand, PRP, rich in growth factors and cytokines, has regenerative effects by stimulating chondrocyte proliferation, extracellular matrix synthesis, and reducing the severity of inflammatory processes.

Comparative studies have shown that PRP is more effective than HA in reducing pain and improving joint function, especially over the long term. However, analyses of side effects indicate that monotherapy with either PRP or HA is associated with a higher risk of mild adverse events (e.g., swelling, post-injection pain) compared to combined PRP+HA therapy.

A review of studies suggests that combining PRP with HA may be the most beneficial form of treatment—offering improved clinical outcomes (pain reduction and enhanced function) while simultaneously lowering the risk of adverse effects. The results of numerous meta-analyses confirm the synergistic effects of both substances and their safety. Combination therapy appears particularly effective in treating moderate to advanced stages of KOA.

Despite promising results, further multicenter studies with standardized treatment protocols and long-

term follow-up are needed to definitively confirm the superiority of PRP+HA combination therapy over monotherapy.

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