REVIEW

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PRP Application in the Treatment of Knee Osteoarthritis: A Comprehensive New Perspective in Light of Current Literature and Clinical Consensus Reports

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Abstract

Knee osteoarthritis is a common chronic joint disease worldwide, representing a significant public health problem because of its impact on pain, functionality, and quality of life. Current treatment options, including pharmacological and physical therapies, aim to manage symptoms in the early and middle stages and delay surgical interventions. Platelet-rich plasma (PRP), an orthobiological treatment, has emerged as a promising treatment offering potential benefits, such as inflammation modulation, cartilage regeneration, and symptom relief. This review evaluates the role of PRP in the management of knee osteoarthritis by analyzing recent literature and consensus reports. The therapeutic effects of PRP are attributed to its bioactive components, including growth factors and cytokines, which promote tissue healing and regulate inflammatory processes. Clinical studies have demonstrated the efficacy of PRP for pain reduction and functional improvement, particularly in patients with mild-to-moderate knee osteoarthritis. However, variability in preparation protocols, dosage, and patient characteristic influence outcomes, highlighting the need for standardized protocols. Key factors such as centrifugation technique, activation method, and leukocyte concentration significantly affect the efficacy of PRP. Consensus reports have recommended PRP as an effective and safe option for the management of knee osteoarthritis, especially in the early and middle stages, and under certain conditions, has potential application in advanced cases. Although PRP shows promise as an innovative treatment, further high-quality, long-term studies are needed to optimize the protocol. This review highlights the efficacy of PRP among conservative treatments and its potential to improve outcomes in patients with knee osteoarthritis.

Keywords: Knee osteoarthritis, platelet rich plasma, PRP therapy, orthobiological treatments, cartilage regeneration, ınflammation modulation

INTRODUCTION

Knee osteoarthritis is the most common chronic joint disease worldwide. It is an important public health problem that causes pain and loss of function, which negatively affects the quality of life of individuals (1). It is estimated that between 7.2% and 16.7% of individuals over 45 years of age in the US experience symptomatic knee osteoarthritis (2). According to global studies, the prevalence of knee osteoarthritis was reported to be 22.9% in individuals aged 40 years and older, with an incidence of 203 per 10,000 person-years (3). As a result of these data, it can be seen that the disease constitutes a significant and increasing burden worldwide.

Knee osteoarthritis is often managed in the late stages with knee arthroplasty, which requires a major surgical intervention and is associated with significant health costs (4). However, conventional treatment approaches, including pharmacological and physical therapies, are available to manage symptoms in the early and middle stages. These approaches also aim to delay surgical intervention. In this context, the need for innovative treatment approaches for knee osteoarthritis is increasing daily.

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In recent years, orthobiologic therapies, particularly platelet-rich plasma (PRP), have attracted attention for their potential to alleviate symptoms, promote tissue healing, and even reverse pathological processes by slowing disease progression. Moreover, orthobiologic therapies are undoubtedly becoming an important player in the treatment of osteoarthritis of the knee as an alternative or complementary option to surgical interventions, with the goals of modulating inflammation, promoting cartilage repair, and improving patients' quality of life.

In the field of orthobiological therapies, the heterogeneity of the evidence level in the existing literature and the lack of standardization of biological treatment protocols increase the importance of constantly updated information and consensus reports. This review examined the role of PRP in the management of knee osteoarthritis in the light of current literature and consensus reports, focusing on the popular use of PRP therapy, and evaluated the efficacy and outcomes of these approaches in clinical practice.

Platelet-rich Plasma (PRP) in Knee Osteoarthritis

PRP is a plasma product derived from the patient's own blood with increased platelet concentration. It has emerged as a promising conservative treatment option for knee osteoarthritis aimed at alleviating symptoms and delaying surgical interventions. Thanks to the growth factors and cytokines it contains, it plays important roles in tissue regeneration, cellular renewal, and inflammation (5).

With PRP application, mainly by cell proliferation with growth factors [such as platelet-derived growth factor (PDGF), transforming growth-β, vascular endothelial growth factor (VEGF), epidermal growth factor], by reducing the effect of catabolic mediators (such as interleukin-1β and metalloproteinases), by providing proliferation and differentiation of mesenchymal stem cells, mechanisms of action such as suppressing the release of inflammatory cytokines (such as interleukin-1 and tumor necrosis factor-alpha), increasing the level of anti-inflammatory cytokines (such as interleukin 10) and limiting matrix degradation while increasing collagen synthesis in the extracellular matrix have been reported in the literature. (6-12).

In preclinical in vitro and animal studies, PRP has been shown to have several heterogeneous mechanisms of action, including chondrocyte proliferation, inflammation modulation, and matrix production (13,14). The effects of these mechanisms have also been reported to increase with the frequency of administration and concentration in both in vitro and clinical studies (15-19). In numerous randomized controlled trials and meta-analyses on the clinical efficacy of PRP, positive effects have been observed, particularly on pain control and functional improvement. According to the ESKKA-ORBIT consensus report, clinical evidence confirms the efficacy of PRP injections in the treatment of osteoarthritis of the knee, and there is consensus that there is sufficient pre-clinical and clinical evidence in the literature to support PRP injections as an appropriate treatment option in patients who do not respond to conservative therapies (20). However, several factors have been reported to influence the efficacy of PRP.

1.Preparation Techniques

PRP preparation methods are critical factors determining the efficacy and safety of the treatment. Although PRP is a plasma product in which platelets are concentrated, the protocols used in the preparation process may cause differences in the cellular and biochemical components of PRP. These differences may affect treatment outcomes.

The open and closed methods

Although there are many methods for PRP preparation, all involve differential centrifugation. There are two main methods: open and closed techniques. Closed techniques are performed in a sterile environment with less risk of contamination, whereas open techniques require more manual intervention and may have a higher risk of contamination (21).

The single and double centrifugation methods

The centrifugation protocol can affect the platelet concentration and the number of other ingredients and can be performed by single or double centrifugation. Double centrifugation provides a higher concentration of platelets and leukocytes than single centrifugation (22,23). It has also been reported to contain higher concentrations of growth factors, such as PDGF and VEGF, using the double centrifugation method (23,24).

Centrifugation speed

The centrifugation speed and time have also been shown to have a significant effect on the homogeneity and concentration of the resulting cellular components (25). Centrifugation at lower speeds has been reported to provide more homogeneous extraction of cellular components (25,26). The available literature shows that PRP preparation protocols are highly variable and most studies do not provide adequate information. The protocol that is emphasized is to perform the first centrifugation at 100-300 g for 5-10 minutes and the second centrifugation at 400-700 g for 10-17 minutes (21).

Activation methods

Activation methods are used to increase the effectiveness of PRP and trigger degranulation of platelets and release of growth factors, which are biologically active molecules in PRP, into surrounding tissues. The most common and well-known methods are performed using activators such as calcium chloride ($CaCl_2$) and thrombin.

CaCl2 mimics the natural activation of platelets, leading to gradual degranulation. Thrombin is a natural enzyme that initiates the coagulation cascade and exerts a short-term effect by rapidly degranulating platelets. In summary, thrombin has an intense and rapid effect, whereas CaCl2 has a more prolonged and stable release (27,28).

Leukocyte-Rich PRP (LR-PRP) and Leukocyte-Poor PRP (LP-PRP)

LR-PRP is a type of PRP in which leukocytes are concentrated along with platelets. The leukocytes in the PRP content have the capacity to secrete inflammatory mediators and proteases. LP-PRP is a form in which leukocytes are removed from the PRP content. This form aims to reduce the levels of inflammatory mediators. Both LR-PRP and LP-PRP improve pain and function in the treatment of knee osteoarthritis (29). However, no significant difference was observed between these improvements (30,31). However, LR-PRP has been reported to have local side effects, such as pain and swelling, with a higher rate of inflammation compared to LP-PRP (29-32). The higher inflammation in LR-PRP than in LP-PRP may cause increased pain in chronic inflammatory diseases.

According to a consensus report, it was reported that, according to the available literature, LR-PRP and LP-PRP are not preferable to either type, and that any type can be chosen in the management of knee osteoarthritis (20).

PRP Injection Volume

It has been reported by the consensus group that the optimal volume (2-12 mL) for PRP injection may have an effect on treatment, but there is no evidence in the literature on this issue and no recommendation can be made at this point (20).

2. Patient Characteristics and Indications

The efficacy of PRP can vary greatly depending on the individual characteristics of the patient and the characteristics of the clinic. Therefore, there are important factors to be considered in patient selection to ensure the procedure is successful.

Age

The effectiveness of PRP treatment varies according to patient age. PRP application protocols are an important factor affecting treatment outcomes. With advancing age, platelet function may decrease, and the release capacity of growth factors may decrease (33,34). In a randomized double-blind study comparing patients with mild to moderate OA to a placebo control group, PRP therapy was most effective in patients aged 51-65 years and reported better results in knee osteoarthritis and in patients with low mechanical axis angle (19). In a study of patients with an average age of 56.1 years, PRP treatment was reported to be more effective than hyaluronic acid or placebo injections (35). In a patient group with an average age of 59.8 years, pain and functional improvement were observed after PRP treatment, and this improvement continued for up to 7 months (36). According to the consensus report, most studies covered a median age of 55 to 65 years, with the consensus that no specific age range can be recommended and that the response decreases with increasing age (20). The consensus group also stated that instead of focusing directly on chronological age, other factors should be considered (20).

Body Mass Index (BMI)

BMI is another factor that may affect the success of PRP treatment. It is known that obesity accelerates the progression of osteoarthritis by increasing the mechanical load on the knee joints. However, there are limited references in the literature evaluating the efficacy of BMI and PRP, and in general, similar pain and functional scores improved at low and high BMI, and the results obtained were independent of BMI (37).

Stage of Osteoarthritis

The efficacy of PRP may differ according to the stage of knee osteoarthritis. According to the Kellgren-Lawrence classification (KL), the stages in which PRP is most effective have been shown in the literature as early and intermediate stage OA (KL: I-III) (18,19,37-39). According to the consensus report, clinical evidence suggests that PRP is effective and indicated for mild to moderate knee OA (KL: I-III) (20). There is also a consensus that advanced stage (KL: IV) can be considered in selected cases (20).

Concomitant Health Problems

Although the general health status of patients is believed to have an impact on the effectiveness of PRP treatment, there is limited information on the impact on comorbidities. In addition to recommendations and contraindications for knee injections, recommendations for additional diseases were reported in the consensus report specific to PRP treatment (20). In addition to contraindications due to local problems, such as infection and skin problems, recommendations have been made for systemic infection, malignancy, inflammatory diseases, and quantitative and qualitative platelet disorders in the blood.

- **Systemic Infection**

It was reported in a consensus report that in the presence of systemic infection, it should be kept in mind that PRP may have a negative effect on the functional status due to the immune and inflammatory processes at the systemic level (20).

- **Malignancy**

Although the risk of tumor proliferation with PRP content has not been reported in the literature, the theoretical risk-caused consensus group considered the presence of both benign and malignant tumors in the knee joint as a contraindication (20). Similarly, there is a consensus that even in the presence of distant malignancy outside the knee, the contraindication should apply until there is more evidence.

- **Inflammatory Diseases**

The presence of systemic inflammatory diseases (such as rheumatoid arthritis) and autoimmune diseases does not preclude PRP therapy for knee osteoarthritis, according to a consensus report (20).

- **Numerical and Qualitative Platelet Disorders in Blood**

It has been reported that the PRP formulation must have an absolute platelet count of 10 billion to have a long-lasting chondroprotective effect lasting up to 1 year in moderate knee osteoarthritis (38). However, there are no specific data on the safety and side effects of PRP therapy in patients with thrombocytopenia or platelet dysfunction. In the report of the consensus group; thrombocytopenia, thrombocytosis, or coagulopathy conditions are stated as relative contraindications because changes in platelet count and function may occur, and it is reported that the optimal platelet count range cannot be defined in PRP content (20).

Patellofemoral Osteoarthritis (PFOA)

In the current literature, it has been reported that pain and functional improvement in patients in the treatment of PFOA with PRP continues for 6 and 12 months, but according to the consensus report, it can be considered an option for treatment (20,39-41).

3. Implementation Protocol

Number of Doses in PRP Treatment

Although there is no clear consensus in the literature, most studies suggest that multiple-dose PRP applications are more effective than single dose injections (42-45). It has been reported that although single-dose PRP applications provide pain and functional improvement in the short term, these effects are not as sustainable as multiple-dose applications in the long term (42,43). However, in advanced knee osteoarthritis, although multiple injections do not provide any benefit, studies have reported that two doses are more effective than a single dose, and three doses are even more effective (18,44,45). The consensus group recommends administering injections at dose intervals of two to four (20).

Dose Range of PRP

Although there is no clear result in the literature on the dose interval in treatment, according to the recommendation of the consensus group, it has been reported that since the activity of degranulate growth factors occurs in the first 3 weeks after injection, it may be appropriate to perform the application at intervals of 1 to 3 weeks (20).

Use of Non-steroidal Anti-inflammatory Drugs (NSAIDs) With PRP

Regarding the use of NSAIDs after PRP injection, the effects of healing may be limited by reducing the release of growth factors (46,47). In addition, decreased platelet function was observed in PRP obtained from patients taking NSAIDs (47). Therefore, the consensus group recommends avoiding the use of NSAIDs up to 2 weeks before and 1 week after PRP application and the use of non-inflammatory drugs (such as paracetomal, dipyrone and tramadol) when necessary (20).

Use of Intra-articular Local Anesthetics With PRP

Although there is no evidence in the literature to clarify the effects of local anesthetics on PRP treatment, in vitro studies have reported the negative effects of local anesthetics on platelet function (48). For these reasons, the consensus report does not recommend the use of PRP injection and local anesthesia, but it is stated that it can be applied subcutaneously without entering the capsule (20).

Corticosteroid Injection With PRP

Specific studies on the combined use of PRP and corticosteroids are limited. However, given that both treatment modalities have their own advantages and disadvantages, combination therapy could potentially provide both short-term and long-term benefits. However, the consensus group recommends avoiding the use of PRP therapy in close proximity to corticosteroid injection and recommends PRP therapy for at least 6 weeks after intra-articular corticosteroid use (20).

Combined Use of PRP and Hyaluronic Acid

Research in the literature on whether the combination of PRP and hyaluronic acid is effective in the treatment of osteoarthritis

of the knee generally shows that this combination generally gives better results than PRP or hyaluronic acid treatments alone (49,50). However, the consensus group stated that more data are needed before recommending the combination of PRP with hyaluronic (20).

CONCLUSION

Numerous clinical and preclinical studies on the efficacy of PRP in knee osteoarthritis have demonstrated the benefits of PRP application, especially in terms of pain control, functional improvement, and delay in surgical interventions. However, considering the heterogeneity of preparation protocols, patient characteristics, application protocols, and other treatment-related factors that affect the efficacy of PRP, the need to optimize the treatment is emphasized. Available data from the literature and consensus reports support the use of PRP as an effective and safe treatment modality, particularly in individuals with mild-to-moderate knee osteoarthritis.

The potential of PRP in clinical practice as a powerful alternative to traditional methods as an orthobiologic approach in the treatment of osteoarthritis of the knee is increasingly being recognized. However, standardization of treatment protocols and evaluation of long-term effects in larger studies are critical for the integration of PRP into clinical practice. In this context, the study of PRP applications in a larger patient group with randomized controlled trials designed to achieve high sensitivity and long-term follow-up will determine the future use of this method in the treatment of knee osteoarthritis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.S., Y.A., Concept: Y.S., Y.A., Design: Y.S., Y.A., Data Collection or Processing: Y.S., Analysis or Interpretation: Y.S., Y.A., Literature Search: Y.S., Y.A., Writing: Y.S., Y.A.

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