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The Role of Platelet-Rich Plasma Therapy in Joint Arthroplasty A Mini-Review

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Abstract

Orthobiologics are playing an increasingly large role in the clinical setting across multiple fields of surgery. Particularly, in the field of orthopedic surgery, the employment of platelet-rich plasma (PRP) therapy in total joint arthroscopy (TJA) has become popular for its prorupted benefits of controlling pain, blood loss, and increased wound healing. PRP was originally used for thrombolytic conditions, however, the aforementioned potential benefits have led to its increased use across various fields of medicine including dermatology, neurosurgery, orthopedics, and sports medicine. Currently, there is a persisting gap in the literature surrounding the mechanism of action of PRP, as well as its true role in increasing positive patient outcomes in the context of TJA. Thus, this review aims to briefly highlight the physiological mechanisms underlining PRP therapy, evaluate recent preclinical and clinical data about its effects on TJA patient outcomes, and to describe its concomitant use in novel orthopedic applications.

Keywords: platelet-rich plasma; total joint arthroplasty; platelet-derived growth factor

Introduction

Platelet-rich plasma (PRP) was first conceptualized in the field of hematology in the 1970s to describe plasma with greater platelet counts compared to that of peripheral blood. PRP was initially used to treat patients with thrombocytopenia through PRP transfusions [1]. In the following decade, the anti-inflammatory properties, cell proliferative characteristics, and wound healing capabilities of PRP had garnered attention from medical fields in cardiovascular surgery, plastic surgery, pediatric surgery, ophthalmology, gynecology, urology, and predominantly in orthopedics and sports medicine [2–5].

In orthopedic surgery, the most common indication for total joint replacement surgery is osteoarthritis (OA) [6]. OA is the leading cause of disability in older adults that results in the deterioration of articular cartilage, bone, and surrounding tissue [7,8]. The physical impairments from OA including pain, joint stiffness, reduced range of motion, joint instability, and lower aerobic fitness can significantly reduce the quality of life in patients with OA [9,10].

The goal of treating OA is to stop and ideally reverse its progression. Current treatments, aside from surgery, are palliative options that relieve pain and improve function, however, these options do not alter the course of disease progression [11]. Total joint replacements are surgical interventions that have been shown to reverse the progress of OA and provide long-term improvement in pain, function, and overall symptomatology [12].

PRP therapy has been shown to be relatively safe for the treatment of musculoskeletal conditions and potentially accelerate or augment the soft tissue healing process [13]. PRP therapy has been shown to support tendon regeneration in sports medicine injuries and addresses aspects of the healing process, including cell proliferation and tissue matrix regeneration, inflammation, nociception, infection, and hemostasis [14,15]. PRP can be applied to the site of injury either through an injection performed in the physician's office or intraoperatively during TJA as seen in Figure 1 below [16].

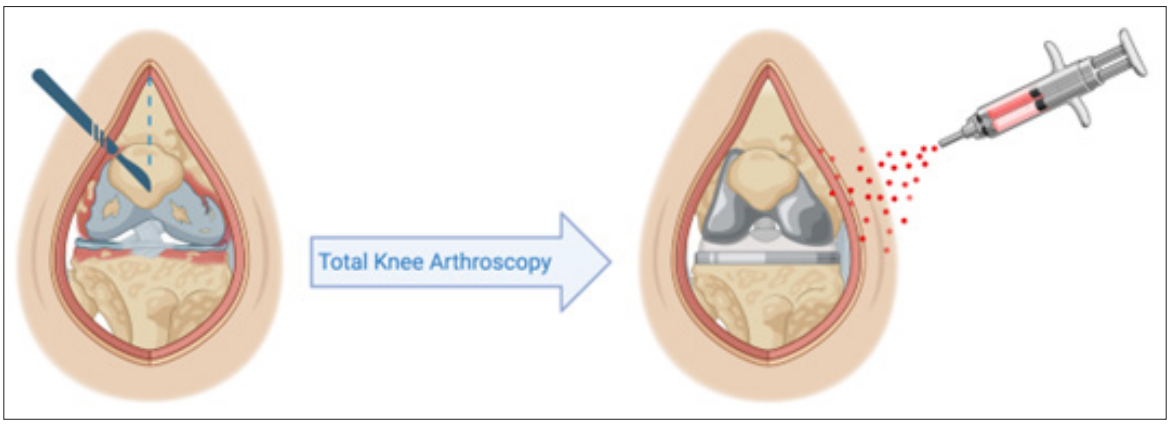

Figure 1: Total Knee Arthroscopy of Osteoarthritic Joint

Total knee arthroplasty (TKA) is one of the most common orthopedic surgeries performed in the US as is associated with significant functional improvements and pain reduction in the osteoarthritic knee. Due to its prorupted healing and hemostatic benefits, platelet-rich plasma (PRP) is intraoperatively introduced into the surgical bed prior to wound closure. Traditionally, PRP is administered through a dual syringe apparatus containing PRP and activating solution, which is a preparation of topical bovine thrombin [17].

While not entirely understood, PRP injections have been shown to improve OA symptoms, delay the need for receiving TJA, and improve outcomes following TJA [18,19]. While PRP therapy in isolation has shown marginal effectiveness, using it in conjunction with surgical intervention shows potential for improved post-operative healing and pain management [20-23]. Thus, the purpose of this review is to briefly highlight the physiological mechanisms underlining PRP therapy and to critically evaluate recent preclinical and clinical data pertaining to patient outcomes.

Biology of Platelet-Rich Plasma

PRP is a supraphysiological concentrate of platelet-rich plasma proteins derived from a patient's own blood. This autologous PRP preparation is made by centrifugation of the patient's blood which is often received from the median cubital vein [24]. Via centrifugation of the sample, this process effectively allows for the separation and removal platelet-poor plasma and the buffy coat— that contains erythrocytes and leukocytes— to increase the concentration of platelets 4-5 times the normal physiological amount [25]. The resulting high concentration of platelets within the sample is thought to promote the healing of soft tissue affected by traumatic and degenerative conditions. These platelets secrete growth factors and are known to facilitate the regeneration of injured tendon structures and other soft tissues [14]. Specifically, platelet-derived growth factors and transforming growth factors (TGF-α and TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), connective tissue growth factor (CTGF), and insulin-like growth factor (IGF-1) have been shown to regulate collagen synthesis, mitogenesis of fibroblasts, stimulate macrophage and neutrophil chemotaxis, induce angiogenesis, regulate endothelial chemotaxis, stimulate protein synthesis, and promote long-term healing [26,27]. As seen below in Figure 1, these platelet-derived growth factors lead to a multiplicity of down-stream cellular effects implicated in hemostasis, inflammation control, angiogenesis, and synthesis of critical extracellular matrix components [28].

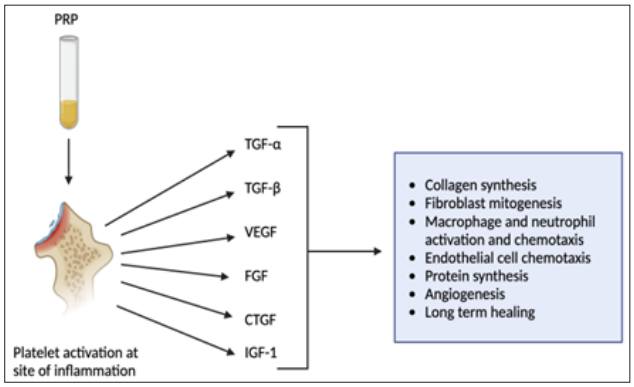

Figure 2: PRP Therapy and Cellular Effects

Following acute injury, there is a healing cascade of events that is principally composed of homeostasis, inflammation, cellular proliferation/matrix biosynthesis, and wound remodeling. Via the introduction of PRP, which is composed of a supraphysiological concentration of platelets, this biologic releases numerous platelet-derived growth factors including TGF-*α*, TGF-*β*, VEGF, FGF, CTGF, and IGF-1. This bolus release of factors is thought to be implicated in promoting the acceleration of the healing cascade via synthesis of extracellular matrix components, scaffold cell mitogenesis, immune cell activation, protein synthesis, and angiogenesis [29].

Platelet-Rich Plasma Therapy in Total Joint Arthroplasty

Due to the unique biological properties described in the previous section, PRP therapy inherently lends itself to therapeutic utility in several clinical scenarios to promote wound healing [30]. Specifically, in the field of orthopedic surgery, evidence suggests that PRP therapy may be beneficial for patients that present with knee osteoarthritis, hip osteoarthritis, and lateral epicondylitis, as well as in the setting of TJA due to said conditions [25,31,32]. In fact, in the US alone, roughly 86,000 athletes are treated with PRP annually[25]. Further, combined with the aging population and expanding indications for younger, active patients, the number of TJAs performed in the US is expected to rise to nearly 4 million by the year

2030 [33,34]. As a result, there is a persisting need for evolving strategies to reduce costs and maintain quality for said procedures [35]. Thus, it is crucial to evaluate the true merit of PRP therapy on TJA patient outcomes, which starts with understanding its dynamic properties in the field of orthopedics.

Physiology of Platelet-Rich Plasma

Particularly, through a process known as dynamic reciprocity, Andia et al. describes the spatial and chemical crosstalk between tissues within the joint as well as between the cells and microenvironment that facilitate these interactions [36]. During injury—such as mechanical insult from surgery—the joint microenvironment is altered and cells such as osteoblasts, chondrocytes, cynoviocytes, and fibroblasts rapidly respond through bidirectional interactions to initiate processes including differentiation/dedifferentiation,proliferation/quiescence, angiogenesis, anabolism/catabolism, apoptosis/necrosis, and inflammation [37]. As seen in Figure 2, this process of dynamic reciprocity is carried out within the confines of the joint via synovial fluid and the bone-cartilage unit as the medium for these interactions [38].

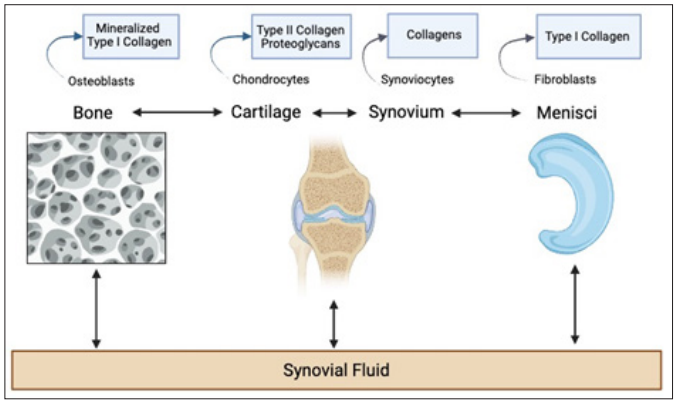

Figure 3: Dynamic Reciprocity

Application of dynamic reciprocity in the context of intra-articular repair aids in the understanding of the complex interactions carried within and throughout synovial joint before, during and after insult. In this concept of cellular interactions, there is bidirectional crosstalk amongst the cells of the joint including osteoblasts, chondrocytes, cynoviocytes, and fibroblasts [37]. These interactions promote the appropriate cellular response to injury/repair and serves as the leverage point for medical interventions such as PRP therapy.

Clinically, through leveraging this natural process, PRP locally modulates the repair and regeneration of damaged articular cartilage in the joints and delays the degeneration of cartilage by platelet-derived growth factor stimulation of mesenchymal stem cell migration, proliferation, and differentiation into articular chondrocytes [39]. Further, PRP is a biological response modifier of the inflammatory nuclear factor-κB (NF-κB) signaling pathway, whereby it reduces pain by decreasing inflammation and angiogenesis of the synovial membrane where pain receptors are concentrated [40]. Finally, PRP has the therapeutic potential to promote tissue regeneration and contribute to articular cartilage lubrication by reducing friction and minimizing secondary chondral damage [28,29]. Cumulatively, these described mechanisms are pivotal in the early successes of PRP therapy in the treatment of osteodegenerative diseases and TJA, nonetheless, further investigation is needed to fully detail the complex relationship between PRP components, wound healing, and their clinical ramifications.

Clinical Efficacy of Platelet-Rich Plasma

Regarding the efficacy of PRP therapy in the orthopedic setting, multiple clinical studies have demonstrated statistically significant improvements in patient-reported pain scores on the visual analog scale (VAS), stiffness, blood loss, and function following PRP treatment when compared to control groups [41-45]. Specifically, Berghoff et al. describes several lines of support for PRP in TJA as their retrospective study reported significantly shorter hospital stays, improved range of motion, fewer units of transfused blood, and improved hemoglobin profiles [17]. A similar study conducted by Mooar et al. found that TJA patients who received autologous PRP experienced a significant improvement in hemoglobin levels (2.68 g/dL vs 3.12 g/dL)—indicative of hemostatic effect—and achieved a significantly higher ROM (79.7° vs 72.1°) when compared to TJA patients whom did not receive PRP [46]. Further, these improvements were reported earlier at 4.35 days versus 6.38 days in these groups, repectively [46].

Although these purported benefits were backed by strong methodology, there remains a relatively high level of speculation surrounding consistent outcome measure. For example, the effect of PRP therapy on the reduction of blood loss and change in hemoglobin levels yielded relatively split results amongst numerous metanalyses, randomized control trials, and larger retrospective cohort studies [19,47-49]. Nonetheless, each of these studies concluded that PRP therapy demonstrated short to medium-term benefits in pain control as well as functional improvements following TJA in patients who received PRP therapy, regardless of hemostatic outcomes.

In addition to improvements in pain and function in the context of TJA, one large metanalyses demonstrated a reduced postoperative retear rate in patients having undergone arthroscopic rotator cuff repair as well as another comprehensive review that demonstrated PRP's ability to stimulate clinically beneficial neovascularization in various musculoskeletal indications [50,51]. Together, these studies allude to PRP's potential employment in cases of chronic tendinopathies in addition to its evolving role TJA.

Altogether, though there is convincing evidence to support the use of PRP, more investigation is necessitated before conclusive deductions can be made on its influence on outcomes in TJA and other musculoskeletal indications. Notably, several limitations were inherent to the studies evaluated, including sample size, patient inclusion/exclusion criteria, differing scoring systems for pain (VAS versus WOMAC), and lack of homogeneity surrounding PRP formulation. Thus, future

research should aim to include large, prospective, randomized clinical trials that thoroughly delineate methodology and longitudinal follow-up for more accurate interpretation of PRP therapy's clinical value.

Limitations and Future Implications of Platelet-Rich Plasma Therapy

Financial and Procedural Challenges

Although PRP therapy provides several prorupted therapeutic benefits, there are a couple of limitations that physicians should be aware of prior to presenting PRP therapy as a treatment option.

One hurdle facing PRP therapy is that most insurance plans do not cover or reimburse for PRP injections, with the average cost ranging from $200 to $500 per injection [52]. Additionally, the Current Procedural Terminology code for PRP injections is 0232T and encompasses harvesting, preparation, and imaging guidance, all of which are billed as one and cannot be separately billed [52]. One study evaluated the cost-effectiveness of PRP use in delaying the need for total knee arthroplasty (TKA) [53]. After analysis, the authors found that PRP injections are not cost-effective after considering both direct and unpaid indirect costs [53]. A lack of clinical efficacy in PRP improving function and reducing pain was the primary limiting factor preventing PRP from being cost-effective [53].

A second set of considerations is the variability in PRP composition, the use of additional factors such as platelet activating factor, and number/timing of treatments [52]. According to a recent meta-analysis of PRP for orthopedic indications, only 61% of studies noted preparation methodology, and within those studies, nine different protocols were used and none reported platelet or white blood cell concentrations [15]. Further, factors such as the preparation device, time and storage methods, and interactions with other biological materials vary between practices and patients [52]. Studies conducted investigating the efficacy of PRP injections are commonly limited by the use of non-standardized PRP preparations [14]. Difficulties in accessing and controlling the concentration of platelets and leukocytes are frequently reported [54]. Variety in the use of commercial systems with different centrifugation machines and protocols also exists [29]. These systems collect different blood volumes, undergo various numbers of cycle revolutions, and report different platelet concentrations [55]. Additionally, some samples of PRP may or may not include leukocytes, which are intrinsically antimicrobial and produce VEGF, further varying the quality of PRP [29]. Furthermore, homogenizing fresh PRP has not yet been adequately described by studies [14].

Novel Indications for PRP in Orthopedics

PRP is traditionally administered in total joint arthroscopy to control pain, blood loss, and promote wound healing. However, new studies are emerging in which PRP is applied in new clinical circumstances.

Particularly, the union of long bone fractures is a complicated mechanism that is influenced by numerous factors, and disruption of any of them may result in nonunion. One study in 2022 investigated the interaction of PRP and extracorporeal shock wave (ESW) in treating long bone nonunion [40]. Cen et al. separated the study participants into two groups: one administered PRP alone and one administered both PRP and EWS [56]. The authors found that PRP combined with ESW was synergistic and would be efficacious in treating nonunion following fracture surgery by improving bone formation while remaining minimally invasive [56].

Further, in the treatment of tendinopathy, corticosteroid injections are commonly used but have been found to have negative effects on tendon homeostasis [57]. PRP has demonstrated cytoprotective effects against corticosteroids on tenocytes, but the combined effects of corticosteroids and PRP have not fully been explored. Hyunchul et. al assessed the effects of PRP with the concomitant use of dexamethasone on tenocytes to further elucidate their interaction [57]. Their results indicated that the inclusion of PRP didn't inhibit the anti-inflammatory effects of dexamethasone, but did substantially mitigate the deleterious side effects of corticosteroids [57]. This study provides a new avenue for approaching tendinopathy but needs further research in clinical patients to ensure its efficacy.

Conclusion

Across the literature, PRP has been shown to release critical growth factors and cytokines implicated in reducing inflammation and promoting local healing of tissues. In the treatment of bone fracture and soft tissue trauma, PRP has demonstrated good outcomes and thus has been used extensively in the field of orthopedics and sports medicine, specifically in the context of TJA. Furthermore, having elucidated the platelet's critical physiological role in the inflammatory, coagulative, and regenerative phases of wound healing, there is more visibility for how PRP therapy has been able to improve tissue regeneration and expedite wound healing. Moreover, the use of PRP in conjunction with other therapeutics such as ESW and corticosteroids has demonstrated increased efficacy and therapeutics benefits, however, these outcomes are currently patient-driven and anecdotal. Finally, differences in platelet concentration exist and a standardized method of preparing and administering PRP has yet to be developed. Thus, further research on preparing homogenous PRP therapy guidelines should be substantiated, and a deeper investigation into its clinical efficacy is warranted through a higher volume of prospective, randomized clinical trials.

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