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OUTCOMES RESEARCH IN ORTHOPEDICS (O AYENI, SECTION EDITOR)

The Clinical Use of Biologics in the Knee Lesions: Does the Patient Benefit?

Ibrahim Fatih Cengiz[1,2] · Hélder Pereira[1,2,3,4] · João Espregueira-Mendes[1,2,5,6,7] · Rui L. Reis[1,2,8] · Joaquim Miguel Oliveira[1,2,8]

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Abstract

Purpose of Review Overview the outcomes of the latest use of platelet-rich plasma (PRP) for the treatment of knee lesions in the clinics and discuss the challenges and limitations.

Recent Findings Recent clinical studies mainly indicate there may be benefit of PRP usage for the treatment of knee lesions. As an autologous source of bioactive components, PRP has been shown to be typically safe, free of major adverse outcomes. The use of PRP has been continuously increasing, and some well-designed, double-blinded, placebo-controlled clinical trials have been published.

Summary Clinical outcomes relating to PRP usage are multifactorial and depend on the severity of the lesion and patient characteristics. Although PRP is safe to use and it can be easily applied in the clinics, case-specific considerations are needed to determine whether PRP could be beneficial or not. If the use of PRP is favored, then, the configuration/optimization of the preparation and administration/delivery strategy with or without a concomitant treatment may further enhance the clinical outcomes and patients' experience.

Keywords Platelet-rich plasma · Knee · Osteoarthritis · Meniscus · Ligament · Biologics

Introduction

Knee joint disorders and injuries are common in orthopedics and can affect millions of people. The knee comprises several different entities with different biology and biomechanics [1–5]. Knee lesions can be asymptomatic or symptomatic with different etiologies that might lead to joint degeneration. Meniscal, chondral, osteochondral, and ligamentous lesions are among the frequent lesions. Orthopedics is a dynamic field that evolves with the basic and applied/clinical evidence while

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✉ Ibrahim Fatih Cengiz
fatih.cengiz@i3bs.uminho.pt

[1] 3B's Research Group, I3Bs – Research Institute on Biomaterials, Biodegradables and Biomimetics, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, University of Minho, AvePark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, Guimarães, Portugal

[2] ICVS/3B's – PT Government Associate Laboratory, Braga, Guimarães, Portugal

[3] Ripoll y De Prado Sports Clinic: Murcia-Madrid FIFA Medical Centre of Excellence, Madrid, Spain

[4] Orthopedic Department Centro Hospitalar Póvoa de Varzim, Vila do Conde, Portugal

[5] Clínica do Dragão, Espregueira-Mendes Sports Centre – FIFA Medical Centre of Excellence, Porto, Portugal

[6] Dom Henrique Research Centre, Porto, Portugal

[7] Orthopedic Department, University of Minho, Braga, Portugal

[8] The Discoveries Centre for Regenerative and Precision Medicine, Headquarters at University of Minho, AvePark, 4805-017 Barco, Guimarães, Portugal

it has the ability to incorporate technological and scientific novelties. Despite the critical advances in science and surgical approaches, the treatments of orthopedic disorders/diseases and managing the associated pain of the patient remain as an outstanding challenge [1, 4, 6–8]. Various repair/regenerative approaches have been applied in orthopedics, including but not limited to cellular therapies with or without supporting biomaterials [1, 6, 9–11], biologics [12, 13], and gene therapy [14, 15].

The current literature indicates that these current strategies have not yet achieved the required efficiency to fully satisfy all clinical needs, and there is a vast room for further research and development. Biologics are biologically active natural components in an isolated or concentrated form such as growth factors, cytokines, stem cells, bone marrow aspirate concentrates, and platelet-rich plasma (PRP). Herein, we evaluate some recent works dealing with PRP and summarized the latest clinical outcomes that have been reported when treating knee lesions.

Platelet-Rich Plasma

PRP is a blood-derived concentrate that is known to enhance the healing of an injured tissue via modulation of cellular signaling pathways [12, 16–18]. Growth factors bind to the specific receptors of the cells and influence the cell activities such as gene expression, growth, and differentiation [19, 20]. Platelets are small cytoplasmic fragments of megakaryocytes in the peripheral blood. Upon an injury, platelets rapidly arrive to the site and release growth factors and mediate the healing process with various proteins in their α-granules [21–23]. This is linked with the recruitment of inflammatory cells and stem cells to the injury site.

PRP is an autologous blood fraction that is prepared from anti-coagulated blood with a supraphysiologic platelet concentration of 1 million platelets/μL or more, while the baseline comprises around 0.15–0.35 million platelets/μL [24–27]. Typical PRP preparation involves the collection of blood from the patient with anti-coagulant followed by centrifugation to separate the red blood cells, platelet-poor plasma, and the buffy coat that contains the white blood cells and concentrated platelets. For leukocyte-poor PRP, the leukocytes needed to be further separated. A meta-analysis of 6 randomized controlled trials [28–33] and 3 prospective comparative studies [34–36] that involve 1055 patients in total indicated that leukocyte-poor PRP might provide better functional outcome scores for the treatment of knee osteoarthritis, than the leukocyte-rich PRP [37•]. However, the dependency of the local adverse reactions on leukocyte concentration was not detected. Platelets are activated by either in situ by contact with collagen, or prior to application for instance by using calcium chloride or bovine thrombin. Upon activation, and degranulation of the α-granules, the growth factors are released. On YouTube (www.youtube.com), there are many step-by-step PRP preparation videos available, as well as on the company (e.g., Harvest Technologies, MTF Biologics, DePuy Synthes Mitek Sports Medicine, Biomet Orthopedics, and Arthrex) websites of the commercially available PRP preparation systems (Appendix 1).

PRP provides various growth factors at physiological proportions for a topical application. The growth factors include platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1). In addition to the growth factors, cytokines, chemokines, adhesive proteins, clotting factors, fibrinolytic factors, proteases, anti-proteases, and anti-microbial proteins are also present [22, 24]. Given the fact that PRP is obtained from the autologous blood, it is intrinsically safe without immune response and disease transmission risk, and it is not carcinogenic since the growth factors do not enter the cell but bind to the receptors on the surface of the cells. Employing PRP to support tissue healing is a rational approach that has been extensively studied in orthopedics (Fig. 1) [13, 38–40, 41••, 42–44].

Filardo et al. [41••] systematically reviewed the in vitro, animal studies, and clinical outcomes of PRP treatment for cartilage lesions and osteoarthritis. Based on the available evidence, potential benefits of PRP is supported by the preclinical studies, it is safe and without major adverse incidents while clinical improvements are good in the short term. Intra-articular application of PRP may contribute to the health of the entire joint, down-regulate the inflammation, relieve the pain, decelerate degenerative events. This systematic analysis also shows that there is an overall pre-clinical advantage of using PRP; however, here are few published high-quality clinical trials, and they indicate a benefit, particularly in young patients without advanced degeneration.

Latest Outcomes: PRP for Ligamentous Lesions, Patellar Tendinopathy, and Meniscal Lesions

Partial anterior cruciate ligament tears in 42 patients were treated by intra-ligament PRP injection (Fig. 2A). 71.1% of the included patients returned to pre-injury sports activity after 5.8 months in average. With a mean follow-up of 33 months, good to excellent outcomes were obtained with the failure rate of 9.5% [46]. PRP has also been used to augment the trephination of the ACL origin [47]. Twenty-four patients were treated, and good to excellent clinical outcomes were reported at a mean of 25.1 M follow-up. However, the lack of a control

Fig. 1 A commercial system (Biomet Orthopedics, USA) for preparation of PRP (A), PRP application on medial collateral ligament (B), PRP application on lateral collateral ligament (C), and ultrasound-guided PRP application (D)

group (i.e., non-PRP group) hinders the contribution of intra-ligament PRP injection.

In a single-blind randomized controlled trial involving a total of 57 athlete patients, with patellar tendinopathy of Blazina stage IIIB, received a single injection of either leukocyte-rich or -poor PRP or saline injection with a subsequent supervised rehabilitation for 6 weeks [48••]. With a single injection, no significant differences in the outcomes were detected between the groups with a follow-up of 12 months. The primary outcome was Victorian Institute of Sport Assessment (patellar; Victorian Institute of Sport Assessment-P) at week 12, while pain during activity and patients' global rating of change were the secondary outcomes [48••].

Lateral discoid meniscus tears of 29 patients were arthroscopically repaired by meniscal suturing with and without PRP injection directly on the repair site with thrombin to form a gel clot [49]. At mid-term follow-up, significant differences in pain relief, functional improvement, or failure rate between the groups were not detected. PRP injections were used to augment allograft transplantation [45, 50] (Fig. 2B). Recently, Zhang et al. [50] reported the outcomes of 31 patients that 90.7% of the patients had significant improvements in all functional and pain score patients have upon treatment.

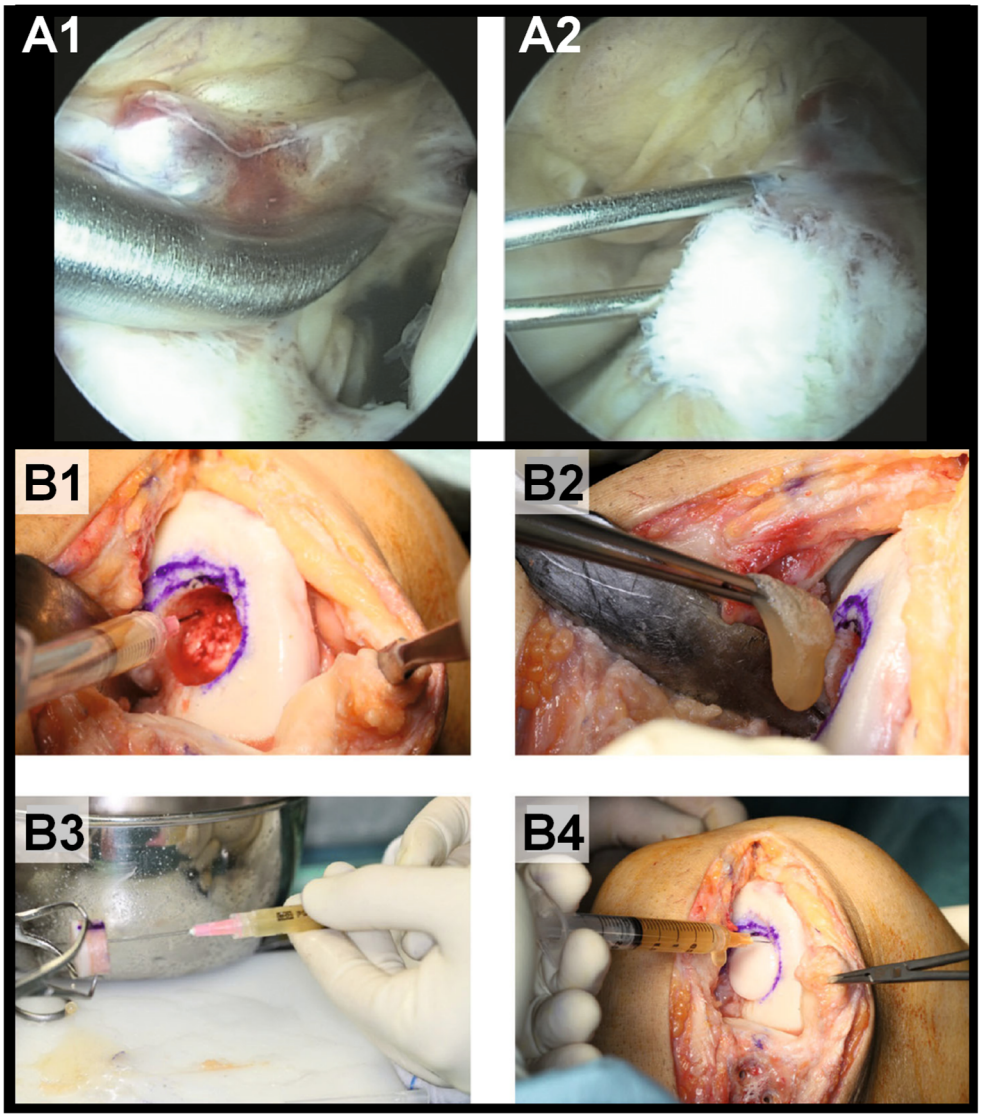

Fig. 2 Healing response technique (A1), and intra-ligament injection of PRP in a partial ACL rupture (A2), (adapted from [39]); infiltration of PRP into subchondral bone (B1), PRP membrane was placed into the wound bed (B2), the femoral plug osteochondral allograft was infiltrated with PRP (B3), sealing the interface around the allograft with PRP (B4) (adapted from [45])

However, since there was no control group, all patients underwent an allograft transplantation combined with PRP injection, the efficacy of the PRP cannot be identified.

In a non-randomized study, platelet-rich fibrin and PRP were incorporated into the arthroscopic meniscal repair of 17 patients, while not in 5 patients in the control group [51]. The groups have similar Tegner Activity Level Scale, Lysholm Knee Scoring Scale, and International Knee Documentation Committee (IKDC); and the improvements with the biologics were not detected. It should be noted that the meniscal tears and their locations were different [51], and this may be one of the factors in evaluating the outcomes [1, 52–54].

In a very recent randomized, placebo-controlled study with 72 patients [55•], improved rate of meniscus healing, better functional outcomes, and higher visual analog scale (VAS) scores were obtained in patients with degenerative meniscus lesions that were treated with percutaneous trephination and PRP injection as compared to patients treated without PRP. The concomitant PRP injection also lowered the need for a future arthroscopy [55•].

In another randomized, placebo-controlled study, PRP-augmented repair of bucket handle meniscal tears ($n = 18$) provided better outcomes than the control group ($n = 17$) that received saline injection [56•]. At intra-repair site, injection of PRP lead to higher meniscus healing than the controls by being 85% and 47% respectively. The scores of IKDC, Knee Injury and Osteoarthritis Outcome Score (KOOS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were better in the PRP-treated group. Assessed with second-look arthroscopy and MRI, the cumulative outcomes indicated that in the PRP-treated group, 14 menisci healed, 3 menisci partially healed, and 3 cases failed;

while in the control group, only 7 menisci healed, with 1 meniscus partially healed, and 9 cases failed [56•].

Latest Outcomes: PRP for Knee Osteoarthritis

In a double-blind randomized trial, 18 patients with knee osteoarthritis with Dejour grades II–IV were treated with injections of bone marrow–derived mesenchymal stem cells with ($n = 9$) and without PRP ($n = 9$) [57]. The KOOS scores were better in both groups; the improvement was higher in the PRP group (22.6 vs. 26.4). The pain, function, and daily activities were improved throughout 12 months follow-up for both patient groups. Inclusion of PRP lead to an improvement in KOOS pain sub-score from 26.5 to 57.1%, in KOOS-quality of life from 22.4 to 30.7%, and 28.0 to 32.2%. However, from the statistical point of view, a significant additional benefit of inclusion of PRP could not be detected within that trial with a small number of patients.

In a trial with 366 younger patients with knee osteoarthritis (18–30 years old) [58], significant alleviation of inflammation was observed after intra-lesional injections of PRP as compared with the placebo [58]. Intra-articular injection of PRP (leukocyte-poor) was compared with oral non-steroidal anti-inflammatory drugs (NSAID) or intra-articular hyaluronic acid for the treatment of early knee osteoarthritis in a randomized controlled trial with a total of 98 patients [59]. PRP treatment provided higher improvement in WOMAC pain and VAS than NSAID and hyaluronic acid treatments as evaluated at 52-week follow-up, while none of the three treatments provided thickening of the cartilage tissue or reduction of Kellgren–Lawrence scores. Upon 3 weekly intra-articular injections of leukocyte-rich PRP, no better overall clinical outcomes were achieved. In addition, no superior symptomatic functional scores or longer effect duration were obtained with PRP as compared with hyaluronic acid injections at any follow-up points based on the long-term clinical results [60••]. The study was a double-blind, randomized controlled trial with patients having chronic symptomatic knee osteoarthritis having Kellgren–Lawrence grade of 0–3 [60••]. It was shown that the reintervention rate at 24 months follow-up was significantly lower in the PRP group (22.6%) as compared with the hyaluronic acid group (37.1%). It should also be noted that at the final evaluation, the PRP group's IKDC subjective score was significantly better than the baseline while the hyaluronic acid group's not [60••]. The superiority of PRP over hyaluronic acid regarding clinical outcomes, pain relief and functional status of the patients, was also reported in another randomized clinical trial with 89 patients that received in total 3 intra-articular injections with a 2-week gap between injections [61]. While in another study with a total of 54 patients, a single injection of PRP or hyaluronic acid treatments performed without a significant difference between each other and both provided significantly better outcomes compared with baseline [62]. To further investigate the synergy of PRP and hyaluronic acid, these were combined and compared with each of them alone and with placebo for the treatment of knee osteoarthritis of a total of 360 patients [63]. Combination of PRP and hyaluronic acid provided improved results (WOMAC, pain, and physical function) as compared with the two components alone.

A non-randomized study with 115 patients with mild to moderate osteoarthritis indicated that intra-articular injection of methylprednisolone prior PRP injection provided better outcomes regarding VAS and WOMAC at 3 months post-treatment when compared with PRP or methylprednisolone alone. However, the differences between groups were not maintained at 12 months follow-up [64]. In another study, 57 patients with knee osteoarthritis were treated with a single large volume (8.8 ± 1.1 mL) leukocyte-poor PRP injection with a short-term follow-up [65]. The results indicated that PRP was beneficial for 84.2% of the patients at 3 months follow-up regarding functional improvement and pain relief; and at 6 months follow-up, the KOOS total score was significantly increased although the MRI analysis did not provide significant differences compared with the baseline. However, there was no inclusion of a control group in the study; thus, the placebo effect should be considered.

Outcomes of intra-articular injections of platelet-rich plasma, hyaluronic acid, and corticosteroids for the treatment of symptomatic early-stage knee osteoarthritis were compared in a randomized controlled study with a total of 120 patients [66]. Compared with the baseline, significant improvements in WOMAC and VAS were observed in all groups. For pain relief, the PRP group provided superior outcomes. At 3 months follow-up, the WOMAC scores were not significantly different between the groups, while at 6, 9, and 12 months of follow-ups, the PRP group had significantly lower (favorable) WOMAC scores compared with the other two groups.

For the treatment of hemophilic arthroplasty of the knee of 22 patients, single intra-articular PRP injection was compared with five weekly intra-articular injections of hyaluronic acid [67]. PRP treatment provided better outcomes regarding pain relief and knee function improvement as compared with hyaluronic acid. PRP also help reduce synovial hyperanemia. The 3 weekly intra-articular injections of leukocyte-poor PRP provided better outcomes in comparison with hyaluronic acid for the treatment of mild to moderate osteoarthritis of the knees (53 patients, 87 knees) as studied in a randomized, double-blind, placebo-controlled clinical trial [68]. At 1-month treatment, all groups including the sham group, showed significant improvements in WOMAC and IKDC as compared with the baseline; while at 12 months, only the PRP group showed functional improvements.

For the treatment of mild to moderate osteoarthritis of the knee with intra-articular injection of PRP, the additional

beneficial contribution of concomitant intra-osseous PRP injections into the subchondral bone was shown in a study with a total of 86 patients [69]. The study also employed hyaluronic acid in one of three groups that are (i) combined intra-articular and intra-osseous injections of PRP, (ii) only intra-articular injections of PRP, and (iii) injections of hyaluronic acid. Inclusion of intra-osseous injections leads to improvements in the subscales of WOMAC and self-reported pain [69]. A study with 30 geriatric patients with moderate to severe osteoarthritis [70] indicated that simultaneous intra-articular and perimeniscal pes anserinus PRP injections can provide favorable proteomic changes and better functional and pain scores. With this method, PRP can be brought in contact with pes anserine tendons, bursa, medial collateral ligament, and medial meniscus [70]. The study recommends the multiple monthly, at least two monthly injections.

Challenges and Limitations

Several challenges and limitations are affecting the clinical outcomes when comparing the results of trials of the PRP and the experience of the patient. These include the following:

- PRP-related issues: Given the fact that PRP is derived from autologous blood, the therapeutic features depend on the donor, and there are significant variations between PRP obtained from different donors [71]. PRP can be prepared either by manual centrifugation or by using one of the commercially available systems which provide different PRPs with different in the number of platelets and leukocyte number [72, 73].
- Patient- and lesion-related issues: The outcomes depend on the type and the severity of the lesions, as well as the age and condition of the patient.
- Placebo effect: Placebo effect can have a clinical meaning [74•], and thus, the inclusion of a placebo group is highly valuable to understand the effects of PRP.
- Contraindications: The contraindications to use PRP include platelet/blood disorders, systemic infections, acute viral infection, hepatorenal syndrome, immunosuppression, and injection site infection [75].
- Study/treatment design-related issues: Regarding the PRP application, there are several considerations to be made, including but not limited to: the preparation method, location of injection, the volume of applied PRP, frequency (single injection or a series of injections with a frequency), use/effects of anesthetics, being applied to augment a surgical procedure, and the presence of any concomitant treatment. Interpretation of the outcomes/treatment effect should be made correctly to avoid misconceptions about the better results compared with baseline [48, 76]. Although the delivery of PRP can be beneficial, its effects are limited, and thus, the lifespan of the platelets and the growth factor release kinetics should be considered to define that last time-point that an effect is expected. It is also highly beneficial to characterize the applied PRP and report it along with the treatment outcomes.

Conclusions and Take-Home Messages

PRP treatments are safe for the patients, and the studies mainly acknowledge its theoretical and practical benefits. PRP has a place for treatment of knee lesions alone, as an augmentation, as a supplementary component of the conventional treatment, or as a part of tissue engineering construct. Several, but not all clinical studies showed a clinical benefit of PRP, particularly for patients with mild-moderate degenerative cartilage lesions of the knee. PRP preparation and application is typically time-efficient and uncomplicated. In addition to the fact that different PRPs can be prepared using different commercial systems and patient response can be dependent on a multitude of factors. Patients respond differently to the bioactive substances, while the lesion types, severity, locations, and etiologies are variable. Nonetheless, the trend in the literature is expected to continue, and more PRP clinical studies will be published. It should be clearly noted that we need well-controlled statistically powered studies to determine the efficacy of PRP in the long term.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This paper does not contain any studies with human or animal subjects performed the authors.

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- •• Of major importance

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