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The Role of Plasma, Platelets, and Growth Factors in Knee Osteoarthritis: The Evidence-Based Medicine 2022

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Knee osteoarthritis greatly affects the quality of life of numerous people worldwide. Study in 2020 estimated that the global incidence of knee osteoarthritis was 203 per 10,000 person-years and the global prevalence was 16%. Biologic derivatives, such as plasma, platelets, and growth factors, have gained popularity due to their efficacy and safety; however, several controversies related to the treatment of knee osteoarthritis with orthobiologics still exist. The purpose of this review is to provide recent evidence about the use of growth factors as orthobiologics for the treatment of knee osteoarthritis, to summarize the up-to-date clinical practice guidelines provided by American Academy of Orthopedic Surgeons (AAOS) and American College of Rheumatology (ACR), and to discuss these guidelines based on the latest research.

Keywords: orthobiologics, plasma, platelets, growth factors, knee osteoarthritis

It is generally recognized that knee osteoarthritis (OA) is caused by mechanical factors; however, the latest studies have shown that this disease could also have biological etiologies[1,2]. As an underlying pathophysiology, a shift from sole cartilaginous degeneration to complex cellular signaling pathways has been proposed[1]. Numerous inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), have been implicated in the catabolic pathways activated during knee OA[3]. The treatment options for knee OA range from conservative therapies to surgeries, with total knee arthroplasty being the last resort, even though it provides promising outcomes[4,5].

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Recently, "biologic" compounds, or biologics, have become the third wave of medications used for the treatment of knee OA, following synthetic and biomimetic compounds as the first and second waves, respectively. Biologics brings patients closer to the concept of personalized and precision medicine where autologous products are extracted from individual patient and are processed to serve customized medical practice[6]. Biologics is a collective term for products that include cells, scaffolds, and growth factors[7]. For example, in the orthopedic field, autologous chondrocyte implantation (ACI) has gained popularity as a cellular component medication, while scaffolds or matrices made from biologic, synthetic, or composite compounds are the examples of scaffold usage for matrix-induced autologous chondrocyte implantation (MACI)[8]. Growth factors, another type of biologics which can now be produced at higher concentrations[7], are presently used as platelet-rich derivatives, such as platelet-rich plasma (PRP), platelet-rich growth factors (PRGF), and platelet-rich fibrin (PRF).

Currently, there are several controversies about the usage of biologics for the treatment of knee OA, particularly as it relates to pain and functional outcomes. The purpose of this review is to summarize the latest evidence about the usage of growth factors for the treatment of knee OA.

Orthobiologics

The American Academy of Orthopedic Surgeons (AAOS) defines "Orthobiologics" as the substances that are autologous-in-origin and are processed to be in higher concentration for speeding up and enhancing the quality of soft tissue healing[7]. Furthermore, orthobiologics products can be used as part of outpatient and inpatient services. Here, we will focus on the use of platelet-rich derivatives, the clinical treatment option that can be offered as an outpatient service.

Knee osteoarthritis

Numerous studies have shown that in patients with radiographic knee OA classified as Kellgren-Lawrence (KL) Grade 0–4 there was a poor correlation between the score and pain, as well as physical functions. Furthermore, it has been proposed that in some patients pain arises from causes other than the structural damage of the joint, which cannot be seen by an X-ray, such as degenerative tear of meniscus, synovial plica, and loose bodies. Therefore, a treatment based solely on knee X-rays would lead to a suboptimal result[9].

Currently, new paradigms in the pathogenesis of knee OA consider the knee as an organ, and all structures surrounding the knee area, i.e., muscle, tendon, synovium, articular cartilage, meniscus, and bone, could be a source of knee pain[2,10-12]. Therefore, treatment options should be based on the definite pathology of the disease whether it is extra-articular or intra-articular. Extra-articular disease, for example, pes anserinitis, should be treated with a proper medication and a rehabilitation program. Intra-articular disease, such as cartilage degeneration, could be one of the candidates for platelet-rich derivatives application, while meniscus or cruciate ligament pathology should be treated accordingly.

Using this perspective, all structures surrounding the knee should be managed with the corresponding treatment at an outpatient setting. For example, muscle weakening has been determined to be one of the sources of knee pain in OA patients[13]. Therefore, patients with knee OA should be advised to perform fixed arc quadricep exercises for muscle strengthening. Using rhinology concepts, since synovial fluid is degraded by time[14], its properties could be improved with intra-articular hyaluronic acid and platelet-rich derivative treatments[15]. Furthermore, it was reported that cartilage lesions were responsive to growth factors treatment *in vitro*[16]; however, further research is necessary to confirm these findings *in vivo*.

Biologics

Platelets

Platelets are a type of blood cells that are generated daily from bone marrow megakaryocytes and have an average lifespan of 8–10 days. Megakaryocytes, 160 μm diameter cells, derive from pluripotent hematopoietic stem cells that are primarily restricted to the bone-proximal osteoblastic niche. Megakaryocytes migrate from the osteoblastic niche to a vascular niche, the region proximal to the blood vessels of the bone marrow cavity. These vascular niches represent dynamic biological scaffolds necessary for rapid platelet production. After reaching the vascular niche, megakaryocytes extend long branching processes and turn themselves to be proplatelets. These proplatelets contain slender tubular projections at their ends which aid in releasing platelets from their tips. A single megakaryocyte can give rise to 1,000-3,000 platelets. Circulating platelets are 2–3 μm in diameter[17]. Platelets contain α-granules, 200–400 nm diameter organelles, which store proteins and growth factors which play important roles in hemostasis, inflammation, wound healing, and cell-matrix interactions. These growth factors include platelet-derived growth factor (PDGF), which induces proliferation of connective tissue cells, transforming growth factor-β (TGF-β), which stimulates proliferation of osteoprogenitors and inhibits osteoblast differentiation and mineralization, insulin-like growth factor (IGF-1), which

promotes the late-stage differentiation and activity of osteoblasts, and vascular endothelial growth factor (VEGF), which induces endothelial cell proliferation and migration[18,19].

Platelet-rich plasma

Platelet-rich plasma (PRP) is defined by the American Red Cross as the processed liquid fraction of autologous peripheral blood with a platelet concentration above the baseline. The rational of PRP utilization in soft tissue repair is mostly based on inflammation. Highly concentrated platelets provide growth factors and proteins necessary for the whole inflammatory processes in the injured tissue which include inflammation, synthesis of new connective tissue, and revascularization[20]. Unfortunately, the lack of consensus on standardization of PRP preparation protocols with adequate reporting on bioformulations in clinical applications, leads to the inconsistencies in reported clinical outcomes. Chahla *et al*. proposed that a detailed, precise, and stepwise description of the PRP preparation protocol should be required to allow comparisons between studies and provide reproducibility[21].

Due to the popularity of PRP in clinical usage, many commercial PRP kits are available. These kits are divided into high-yielding systems, which provide 3–10 times platelet concentration compared with baseline, and low-yielding systems, which provide only 1–3 times the concentration. High-yielding devices include GPS II and III (Biomet Biologics, 3–8 folds), SmartPRep (Harvest Terumo, 4–6 folds), Magellan (ArterioCyte Medical Systems, 3–7 folds), and Alpas (6–13 folds). Low-yielding devices include Arthrex ACP (Device Technologies, 2–3 folds), Cascade PRP therapy (1.3–1.7 folds), and Regenkit (1.6 folds)[22-24].

Classification system

Since there are no consistent PRP preparation protocols, different classification systems have been proposed. For example, Ehrenfest *et al*. first classified PRP based on three main variables: platelet, leukocyte, and fibrin content, resulting in four main categories of PRP: pure-PRP (P-PRP), leukocyte-rich PRP (LR-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte-rich PRF[20]. Later, Delong *et al*. proposed a classification called "platelet, activation, white blood cells", or PAW, based on the absolute number of platelets, which included four ranges of platelet concentrations, the use of platelet activators, and the presence or absence of leukocytes[25]. Depending on the spinning method, PRP preparations could be also divided into single-spin and double-spin techniques, which would provide different laboratory outcomes and will be discussed later in this review[26]. Since leukocytes are thought to have an impact on the intrinsic biology of chronic tissue lesions due to their immune properties, some PRP classifications are based on leukocyte content, for example, leukocyte-rich (LR-PRP) and leukocyte-poor PRP (LP-PRP)[20]. Depending on the preparation method and leukocyte content, some classifications are based on PRP components, such as buffy coat-based PRP and plasma-based PRP. PRP systems that use a buffy coat contain a higher concentration of white blood cells compared to baseline levels, whereas plasma-based methods provide lower concentration of white blood cells compared to baseline levels[27].

In 2017, Lana *et al*. proposed MARSPILL classification, which stands for M-method of preparation, A-activator, R-red blood cells, S-spinning method, P-platelet enrichment, I-image guidance, L-leukocyte content, and L-light activation. Methods of platelet-rich product preparation consist of an in-house or a commercialized production. Activation process is not mandatory therefore it divides platelet-rich products producing process into the presence and absence of activator. The presence or absence of red blood cells also provides different types of platelet-rich products. Spinning methods consists of single or double spinning techniques. Platelet concentration in platelet-rich product is normally compared to baseline whole blood for their enrichment characteristic. Image guidance can be used as an application to enhance accuracy of biologic products injection. Like other previous classifycation, platelet-rich product can be divided into leukocyte-rich and leukocyte-poor products according to the leukocyte content compared to

baseline whole blood. Light activation recently came to be another source of platelet-rich product activator[20,28].

Platelet concentration in PRP

The optimal platelet concentration in PRP has been extensively debated[29]. The American Red Cross does not provide the exact fold number that platelet-rich derivatives should reach after preparation compared to the peripheral blood baseline. Not surprisingly, studies showed that different preparation techniques lead to different platelet concentrations. For example, the single-spin method provides a lower platelet concentration compared to the double-spin technique[26]. Weibrich *et al*. showed that highly concentrated platelets (11 folds) had an inhibitory effect on osteoblast activity when compared to a lower concentrated platelet[30].

White blood cells in PRP

Although the presence of white blood cells has long been perceived as a sign of inflammation, the role of white blood cell in PRP has been debated. Riboh *et al*. reported that LP-PRP administration significantly improved the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score compared to both placebo and hyaluronic acid (HA), while LR-PRP did not[31].

White blood cells are defined as peripheral blood mononuclear cells (PBMCs) that contain lymphocytes (T and B), natural killer cells, and monocytes, which, in turn, can differentiate into macrophages after their migration into tissues. Macrophages can be polarized into two major phenotypes: M1 and M2. M1 macrophages are proinflammatory cells which play a role during the early phases of the healing process, while M2 macrophages are anti-inflammatory cells which play a role in the late phase of the healing process. This phenotype polarization is regulated by the tissue microenvironment and cytokines, such as IL-10. Lana *et al*. suggested that LR-PRP could exert detrimental effects due to its catabolic activity, while the use of LP-PRP in acute injuries could result in excessive scar formation due to the strong potential of inducing unwarranted anabolic effects[28,32].

In 2021, the latest AAOS guidelines suggested that LR-PRP and LP-PRP treatments could have different effectiveness when used to treat knee OA. While the number of studies is limited and the choice between LR-PRP and LP-PRP is still inconclusive, at this time, AAOS appears to prefer the LR-PRP treatment[33].

Activator in PRP

Exogenous activation of platelets results in rapid coagulation and quick clot formation. Therefore, all PRP products can be activated by the addition of exogenous materials or by contact with endogenous factors[22]. Chemical activators, such as thrombin and calcium chloride, are usually used. Recently, light activation, which involves the exposure of platelets to ultraviolet (UV) radiation, has also been proposed[22].

Endogenous activation provides a slower aggregation of platelets and the release of growth factors. Futa *et al.* studied the difference in clot retraction between collagen-activated clots and thrombin-activated clots in platelet-rich derivative utilization. They found that the collagen-activated clots retracted 50% in the first 24 hours and stabilized over 10 days while the thrombin-activated clots retracted over 90% in the first 24 hours. The delay in clot degradation by endogenous activation may be an advantage in wound healing process of platelet-rich derivatives[34]. Regarding cytokine release, type I collagen as an endogenous activator of PRP also provided a more extended and overall greater release of TGF-b than thrombin *in vitro*[25]. These findings suggest that using fibrin prepared from the platelet-rich concentrate as the endogenous activator in PRP would be the preferred product for patients with knee OA.

Recent evidence-based guidelines

The AAOS 2021 evidence-based clinical practice guidelines for the management of knee OA stated that PRP may reduce pain and improve function in patients with symptomatic knee OA;

however, due to the heterogeneity of the results, inconsistent evidence from low quality studies, and the differences between early- and late-stage OA results, the recommendation is limited and is downgraded to two out of four stars. The recommendation may change based on future research on the use of PRP for the different levels of OA severity. The guidelines highlighted the prolonged effect of intra-articular PRP over intra-articular hyaluronic acid. The guidelines also emphasized the long-term benefits of intra-articular PRP, which appears to be cartilage-protective, while intra-articular corticosteroid administration is associated with cartilage damage over time[33].

At the same time, according to the American College of Rheumatology 2019 guidelines for the management of hand, hip, and knee OA, PRP treatment is not recommended to be used by patients. The heterogeneity and lack of standardization of the available PRP preparations are the main concerns[35]. To evaluate both clinical practice guidelines, here, we provide a summary of the latest meta-analyses, systematic reviews, and clinical trials published after March 2019.

In a systematic review and meta-analysis, Johal *et al*. reported that the use of PRP for knee OA is preferred over placebo, steroid treatment at 3 months, and hyaluronic acid administration at 12 months. These authors also analyzed the characteristics of PRP that could influence the effectiveness of the treatment, including the leukocyte concentration, platelet concentration, and the use of an exogenous activating agent. At 3 and 6 months, the differences in those three parameters did not affect the outcome; however, at 12 months, the platelet concentration and the use of exogenous activation provided a greater effect on different outcomes: PRPs with platelet concentrations greater than 5 folds provided favorable outcome than those with less than 5 folds. Furthermore, PRPs without the use of exogenous activation provided a better outcome than those with the use of exogenous activation, while the leukocyte concentration did not affect the outcomes of PRP administration[36].

Nie *et al*. performed a meta-analysis of randomized controlled clinical trials to indirectly compare the effect of LP-PRP and LR-PRP on pain and functional outcome. The results of this meta-analysis demonstrated that LR-PRP provided better function outcome compared to LP-PRP[37].

Current clinical practice and evidence-based medicine in Thailand

Currently, in Thailand, platelet-rich derivatives have been increasingly studied in leading academic institutes and are used in treatment of knee osteoarthritis and sports medicine.

In 2019, Turajane *et al*. performed a clinical trial investigating the efficacy of PRGF in knee OA patients who failed conservative treatment. Their results at 3 months follow-up showed that only 5.6% of patients with KL Grade 2–3 and 10.8% of patients with KL Grade 4 needed surgical intervention[38]. In 2020, Turajane *et al*. performed another randomized, controlled trial comparing clinical outcomes of IA-platelet plasma concentrate and growth factors and intra-articular corticosteroid injections for the treatment of knee OA. Their results showed a significant statistical difference at 6-12 months between International Knee Documentation Committee (IKDC) and WOMAC scores in favor of platelet plasma concentrate and growth factors injection, with no significant difference at the first two months[39].

In 2021, Ngarmukos *et al*. compared patients with knee OA who received either two or four intra-articular injections of PRP at six-week intervals and evaluated the changes in synovial cytokine levels and clinical outcomes. The authors reported that there were no changes in the levels of synovial pro-inflammatory and anti-inflammatory cytokines, as well as growth factors, after PRP injections; however, starting at 6 weeks and up to 1 year after the injections, clinical outcomes were improved regardless of the number of injections[40].

In a recent (2022) study, Riewruja *et al*. evaluated the cytokine profiles of PRPs from patients with knee OA. The authors demonstrated that the levels of proinflammatory cytokines were significantly higher in PRP than those in the platelet-poor plasma (PPP). The authors proposed

that the presence of proinflammatory cytokines could be responsible for the initiation of the cartilage repair process that preceded the release of anti-inflammatory cytokines and growth factors necessary for tissue healing. Furthermore, Riewruja *et al*. investigated the effect of PRP on chondrocyte proliferation *in vitro* and showed that PRP, compared to PPP and fetal bovine serum (FBS), significantly increased the proliferation of OA chondrocytes. The clinical evaluation of intra-articular PRP injections into the knees of OA patients showed that overall physical performance tests, including sit to stand, time up and go, and 3-minute walk, were significantly improved after 18 weeks of treatment. In addition, the visual analog scale (VAS) score of patients with knee OA was significantly decreased after the intra-articular PRP injection[41].

CONCLUSION

In summary, the application of platelet-rich derivatives as a therapy for knee OA treatment is gaining momentum, since this promising biologic treatment appears to provide better results than steroid and hyaluronic acid injections. However, there are still several important factors that need to be addressed, particularly leukocyte concentration, the use of endogenous activators, as well as the improvement of standardized protocols. Finally, health economics, such as short-, intermediate-, and long-term costs associated with the use of orthobiologics, should also be investigated.

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