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THE USE OF PLATELET-RICH PLASMA IN OSTEOARTHRITIS AND FRACTURES

Gollapudi Akhil*, Kasukurthi Daniyel Raju, Shaik Shabbir and Chandu Babu Rao.

Priyadharshini Institute of Pharmaceutical Education and Research, 5th mile, Pulladigunta, Guntur-522017. Andhra Pradesh, India.

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Abstract

In order to promote and enhance bone healing, biologic drugs have been studied and used recently. Plasmon rich plasma, or PRP, is one of these substances that is becoming more and more popular as an emerging tactic. Examining the available research on PRP injection use and clinical efficacy—particularly with regard to treating non-union fractures—is the primary goal of this study. Recent Discoveries Even though level IV evidence predominated, most published research claimed that PRP sped up the healing of fractures. Currently impeding the successful clinical translation of platelet-rich plasma (PRP) as a therapy for non-union fractures is the absence of randomized, clinical trials (level I-II evidence). Its ability to cure non-union fractures, either on its own or in conjunction with other therapies, has been reported to be promising. Entire text The effects of delivering larger volumes of PRP (i.e., 5–20 mL) and the necessity of longer (> 11 months) randomised clinical trials are two future recommendations that should help accelerate clinical translation and adoption of PRP as a therapeutic. minimum negative consequences.

Keywords: Bone healing. Fracture. Non-union. Platelet-rich plasma (PRP).

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*Corresponding Author

Gollapudi Akhil

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Introduction

Rheumatic diseases (RD) are a spectrum of autoimmune conditions that can cause damage to the musculoskeletal system as well as other vital organs, such as the heart, lungs, kidneys, and central nervous system. Rheumatic diseases are becoming increasingly common due to longer life expectancy and an aging general population, with a prevalence of about 1 in 4 adults in the United States (1). The Center for Disease Control has newly predicted that their occurrence will likely continue to increase by 49% by 2040. There have been significant advances in the study and understanding of pathophysiologic mechanisms and therapeutic interventions involving RD over the last few years. Through the growth of the medical armamentarium involving the use of glucocorticoids, disease-modifying ant rheumatic drugs (DMARDs) and newer synthesized biological immunomodulation agents, physicians are now able to positively impact the prognosis, quality of life,

and functional capacity of these patients. However, despite the progression of available therapies, some limitations persist, *Address correspondence to this author at the Department of Rheumatologic and Immunologic Disease, Cleveland Clinic, Cleveland, OH, United States and many patients are often not suitable for long-term organization due to lack of lasting efficacy, side effects, cost, and lack of insurance coverage, all of which can contribute to discontinuation and suboptimal outcomes. One potential treatment option that has not been well investigated or FDA-approved in RD is the use of platelet-rich plasma (PRP). PRP is an autologous blood product composed of a processed liquid fraction of peripheral blood with a platelet concentration above the baseline(4). The exact mechanisms by which PRP exerts its clinical benefits are unclear. It is believed to stimulate the expression of anti-inflammatory molecules in high concentrations. These molecules include growth factors, such as vascular endothelial growth factor (VEGF), Transforming growth factor- β (TGF- β), epidermal growth factor (EGF), fibroblast growth factor (FGF), and platelet-derived growth factor.

One of the interventions that has gained significant popularity over the past decade is platelet-rich plasma (PRP). PRP is an autologous product derived from whole blood that contains elevated platelet levels, as well as higher concentrations of growth factors, including platelet-derived growth factor (PDGF), transforming growth

factor b, and vascular endothelial growth factor. There are several PRP collection protocols and preparation characteristics available from many commercial systems. The main steps involved in the production of PRP are shown in Figure 1. Generally, the production of PRP requires the collection of whole venous blood, which is then mixed with an anticoagulant prior to centrifugation. A single or double centrifugation process is then performed to separate the erythrocytes and concentrate the platelets. The concentrated platelets are found with leukocytes in the “buffy coat,” from which various methods can be used to isolate the platelets with or without leukocytes. The platelets can then be activated with calcium chloride or applied directly without activation.

platelet-rich plasma (PRP) can be categorized into several different types based on differences in platelet isolation and activation method, centrifugation speed, and collection systems—and multiple classification systems exist. One important categorization of PRP is into leukocyte-rich or leukocyte-poor PRP, defined as having a leukocyte absorption above or below the baseline, respectively. The presence of leukocytes has been associated with elevated catabolic cytokines, which may partially antagonize the anabolic cytokines contained within platelets. Regardless of the preparation system, PRP universally contains supra physiological amounts of platelets and growth factors and has been shown to have an overall anti-inflammatory effect (2) and a positive effect on chondrogenesis, (33) indicating its use as a therapeutic intervention for OA.

While multiple studies have been performed to look into the use of PRP to treat knee OA, there have been fewer looking specifically at hip OA, recommended to be kept distinct from knee OA by the European League Against Rheumatism because of differences in anatomy, advance, and treatment applicability. Studies that do focus on hip OA have varying conclusions, with controlled studies typically using a comparator of hyaluronic acid (HA)—itself an emerging injectable. Therefore, the aims of this systematic review and meta-analysis were as follows: (1) Assess the efficacy of intra-articular PRP on patient-reported outcomes for hip OA; (2) determine the duration of efficacy after PRP injections; (3) assess the influence of composition and dosage of PRP on efficacy; and (4) review the incidence of adverse effects from PRP therapy.

Table 1: organization of non-union fractures adapted from Panagiotis

Classification	Description/pathology
Hypertrophic (hypervascular, viable, vital)	Inadequate immobilisation, yet adequate blood supply. In radiographs, callus formation is decreased with an elephant-foot or horseshoe configuration observed.

Atrophic (avascular, non-viable, avital)	Poorly vascularised non-union, resulting in poor potential for forming bone cells and, therefore, delayed healing. There is little callus formation around the fibrous tissue-filled fracture gap.
Oligotrophic	The body can initiate a healing response but is unable to complete the fracture formed between the two ends of the bone.
Septic Pseudoarthrosis	Abacterial infection impedes the healing process. Typical bacterial strains that inflict non-union sites include coagulase negative Staphylococcus spp. and Propionibacterium spp.
pseudoarthrosis	Persistent motion at fracture site causes formation of false joint (joint that develops at the site of a fracture), often producing synovial fluid.

PRP and Its Role in Regeneration:

The use of PRP in tissue regeneration is a rapidly evolving area for both clinicians and researchers and is being employed in various fields, including osteoarthritis, rotator cuff repair and bone regeneration. This is because autologous platelet concentrations offer an easy, cost-effective method to obtain the high concentrations of specific growth factors including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF beta 1 and 2) and insulin-like growth factor (IGF-1) which are required for tissue healing and regeneration (3). A healthy individual has a baseline platelet count between 1.5 and 4.5×10⁵/μL (4) to be deemed as therapeutically beneficial, a platelet concentration of 4–5 times that of baseline should be present. The preparation of PRP varies slightly in published literature. However, in general, blood is drawn into a tube which is often treated with an anticoagulant. This is followed by centrifugation and activation of the platelets via a chemical agent. Frequently used activators include calcium chloride and bovine or autologous thrombin. Thrombin forms a gel-like substance, from which the PRP can be extracted and directly applied to the patient intravenously. Within platelets are granules, which contain numerous growth factors and cytokines that are important in the early stages of bone repair. On activation, following clotting, these platelets release these growth factors, which play a serious role in the production of proteins required for regenerative processes, such as cellular proliferation, matrix formation, osteoid production and collagen synthesis.

Current use of PRP IN Non-Union Fractures

Clinical trials have investigated the effect of PRP on non-union healing alone (5) and in combination with other forms of treatment such as the use of mesenchymal stem cells (MSCs) internal fixation and/or nailing (6) When using PRP in isolation to treat a non-union, the therapeutic benefit is divided; in some instances, PRP has been

deemed successful in achieving bony union at the fracture site within 11 months of initial injury or surgery. In addition, PRP has been shown to enhance the healing of non-unions when used in conjunction with other forms of treatment such as the 'gold standard' autologous bone graft (8), as well as MSCs and internal fixation. Despite the majority of literature reporting the success of PRP in accelerating healing, it has been found to have less of an effect when compared to other forms of treatment, most importantly the use of bone morphogenetic proteins (BMPs), such as rhBMP-7. This is most likely due to the low concentration of growth factors which can be extracted with PRP in comparison to BMPs

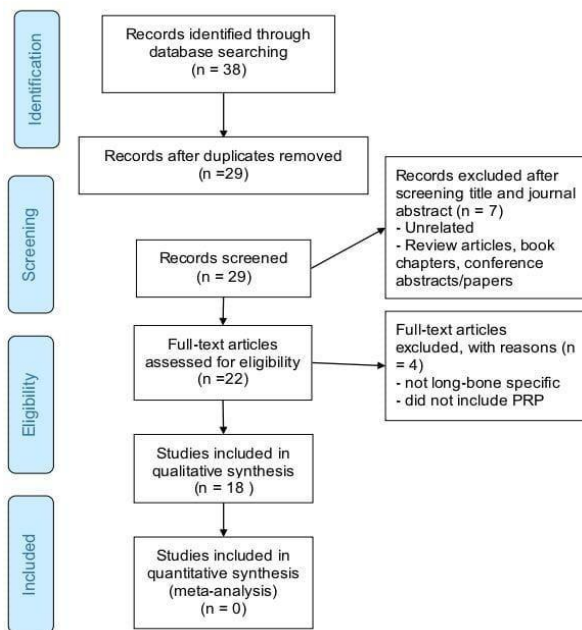


Fig.1: PRP in non-Union Fractures

Among the literature concerning the use of PRP specifically for the treatment of non-union lack of prospective randomised clinical trials (RCTs) and, therefore, a minimal amount of literature with level I-III evidence. Instead, studies are predominantly in the form of case series or preliminary studies (level IV evidence). The advantage of case series is that they are relatively easy to conduct whilst requiring less time and financial resources in comparison to RCTs, cohort or case-control studies. However, the limitations include a lack of control subjects, which leaves the interpretation of results open to bias. Not only are the majority of published PRP studies case series, but the studies are also predominantly pre-clinical. Fortunately, the most recent literature (10), summarised by Roffietal. (9), demonstrated that studies are moving towards a more clinical direction, which is vital for successful translation of any therapy.

Pre Preparation and Administration:

Despite PRP being widely used for several musculoskeletal pathologies(9), there is currently a lack of standardisation with regard to the how PRP is prepared and delivered for treatment of non-union fractures. In general, the PRP preparation process involves the

processes of collection, centrifugation to separate out the platelets, extraction of platelet-rich plasma from the red blood cells and platelet poor plasma and activation using an anticoagulant agent (although this is not always the case) followed by administration to the injury site.

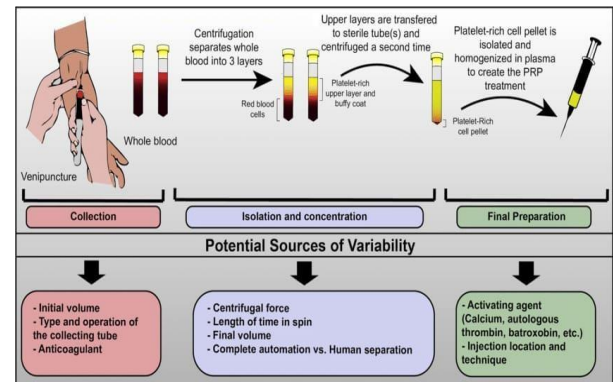


Fig.2 A generalised overview of PRP process

During preparation, the process of centrifugation is utilised for concentrating platelets in all literature. However, the rates of centrifugation differ between studies, ranging from 3200 up to 5200 rpm, which leads to different relative forces depending on rotor length, while other studies do not state the rate. Furthermore, centrifugation can potentially lead to the fragmentation of the platelets and the early release of growth factors which will ultimately reduce the bioactivity of the PRP. Thus, activation of the PRP could be influenced by the relative centrifugal forces between studies causing unwanted variation. Therefore, it is recommended that future studies consider ultrafiltration, which potentially offers a more standardised process for PRP extraction. Activation of PRP via the use of chemical anticoagulant agents is also a key component of the preparation process. Throughout the literature, this activator varies, with thrombin, calcium chloride and calcium gluconate being the most common. Thrombin is often combined with calcium chloride (CaCl₂) or calcium gluconate in an attempt to further increase activation of the platelets. In some literature, details regarding activator use are absent, with some studies using none at all. Different reagents have differing half-lives (12), which also has an impact on the duration of the anticoagulant to clear the system. This in turn will have an impact on PRP activation and, therefore, have an impact on the rate of bone regeneration and PRP efficacy. Furthermore, anticoagulant use, particularly those with prolonged half-lives, may limit the suitability of PRP as a therapy for some patient groups including those with anaemia and renal diseases(13). When analysing PRP delivery methods, it was noted that the volume of PRP delivered varies significantly between studies, with the dose of a single injection varying from

2.5 ml (9) up to 20 ml. The total dose is usually given to a patient as a single dose, but may also be divided into multiple injections over consecutive weeks. This will likely cause differing levels of efficacy between methods of

application as injecting a single dose in comparison to the same dose being divided over several weeks will impact upon the rate of bone regeneration. Dividing a set dose over a period of several weeks will likely delay the intended effect of the injection, slowing the rate of non-union healing. Conversely, the application of multiple equivalent doses of PRP over prolonged period may increase healing rates, although it is impossible to say for certain since rate of healing is patient specific and RCTs would need to be performed to clarify this.

The Impact of PRP Activation on Bone Regeneration

The majority of published studies currently fail to report key aspects such as platelet concentrations, leukocyte components and activation modalities. This is despite Chen et al. demonstrated how a medium concentration of PRP ($2.65 \pm 0.2 \times 10^9$ /mL) induces oestrogenic differentiation of bone marrow stem cells (BMSCs/BM-MSCs), improving fracture healing, whereas a high concentration of PRP ($8.21 \pm 0.4 \times 10^9$ /mL) can inhibit osteogenic differentiation and delay callus remodelling. Labibzadehetal. reported that leukocyte rich PRP induced higher proliferation of BMSCs while other literatures have found activation modality to influence the molecules released by the PRP. This highlights that differing concentrations and ultimately levels of activation will affect the efficacy of the therapy.

Results

1.Rheumatoid Arthritis

Inflammatory arthritis, or rheumatoid arthritis, generally occurs when the body attacks itself by making antibodies against itself. Antibodies are proteins, made by the immune system, that fight microorganisms such as bacteria that invade the body. In these instances, this inflammation is counterproductive because the body is reacting against its own immune system. Rheumatoid arthritis treatment involves use of medications that inhibit tumor-necrosis

factor such as Enbrel and Humira (or generics etanercept and adalimumab) which have been shown to enhance quality of life and slow the arthritic process.

Tumor-Necrosis factoris cell signalling protein (cytokine), which communicates the commands to create inflammation in Rheumatoid arthritis joint swelling. The medical thinking is if you can block TNF and other inflammatory factor production or at least inhibit it, joint swelling will be reduced and hopefully the amount of articular cartilage breakdown resulting from a toxic, over inflamed joint environment will be slowed. Medications have shown that they indeed can slow and reduce inflammation, however, the articular cartilage still breaks down even as the medications become more sophisticated.

- ✓ In the present study, the therapeutic effects and primary mechanism of PRP on a type II collagen induced arthritis mouse model was investigated.
- ✓ The therapeutic efficacy of PRP in this study

demonstrated that treatment with PRP alleviated arthritis and reduced humoral and cellular immune responses.

- ✓ Mice treated with PRP exhibited downregulated expression of various inflammatory markers including the interleukin family of immune system stimulators (inflammatory) IL-6, IL-8, IL-17A, IL-1 β , TNF- α , receptor activator for nuclear factor κ B (regulates and creates messages to begin inflammation) and -IFN γ - (interferon) in inflammatory tissue.
- ✓ In addition, healing factors listed below were shown to increase:
- ✓ Vascular Endothelial Growth Factor (VEGF) Helps new blood vessel formation, thereby increasing vascularity in injured areas,
- ✓ Platelet-Derived Growth Factor (PDGF) Attracts immune system cells to the area and stimulates them to proliferate. Has been shown to enhance ligament and tendon healing.
- ✓ Transforming Growth Factor- β (TGF- β) Secreted by and affects all major cell types involved in healing. Similar affects as PDGF.
- ✓ Insulin-like growth factor-1 (IGF-1) a growth factor mediator.

2.Systemic Sclerosis

Pityriasis rubra pilaris (PRP) is a rare, chronic erythematous squamous disorder of unknown etiologic. It has been found in association with several autoimmune diseases, including thyroiditis, myositis, myasthenia gravis and vitiligo. Herein we report a case of systemic sclerosis in a patient with classic adult pityriasis rubra pilaris. A 38-year-old woman with classic adult type 1 pityriasis rubra pilaris (PRP) developed progressive skin thickening of the trunk, face, upper and lower extremities after 2 years of PRP treatment with topical emollients and steroids. Clinical examination and immunological findings were consistent with SSc. Co-existence of these two rare conditions is documented for the first time.

It has been suggested that toxic oxygen free radicals can be involved in the pathogenesis of systemic sclerosis (scleroderma) (SSc). Because the cells that contribute to the generation of free radicals are not known, our aim was (i) to evaluate the ability of unmanipulated and polymorphonucleate neutrophils of SSc patients to generate superoxide anion ($O_2^{\cdot-}$); and (ii) to investigate whether the $O_2^{\cdot-}$ produced by these cells involved the activation of nicotinamide- adenine dinucleotide diphosphate oxidase biochemical pathway. Employing the superoxide dismutase-inhibitable reduction of cytochrome c to evaluate the generation of $O_2^{\cdot-}$, unmanipulated monocytes of SSc patients generated more $O_2^{\cdot-}$ than primary Raynaud's phenomenon patients and normal control monocytes ($p=0.0001$), and the release was higher in patients with diffuse cutaneous involvement

and 5 y or less disease duration ($p = 0.02$). The involvement of nicotinamide-adenine dinucleotide diphosphate oxidase in the enhanced O_2^{--} production was demonstrated by the finding that the cytosolic components of the enzyme, P47phox and p67phox, were both translocated to the plasma membrane of enriched but otherwise manipulated monocytes of SSc patients.

3. Sjogren's Syndrome

Sjogren's syndrome is an autoimmune disease that can manifest plenty of symptoms, up to and including hair loss. Commonly occurring with other conditions like lupus, scleroderma, or rheumatoid arthritis, it's something that affects millions of people throughout the world. And while it can cause significant disruptions to your quality of life (even without other complications), it's the aesthetic changes like hair loss that can drastically affect your self-esteem.

But can PRP injection treatment help with hair loss caused by Sjogren's syndrome? While the evidence we do have is promising in regards to how PRP injection treatments can help with Sjogren's-induced hair loss, the exact efficacy of PRP therapy makes the overall effects a little unclear. You can experience some hair regrowth and rejuvenation with PRP treatments – but how much will depend on plenty of other factors.

One thing to keep in mind is that while patients with Sjogren's syndrome can experience hair loss, it's not always clear that this is caused by Sjogren's itself. Autoimmune disorders cause the body to attack itself, and this can often cause plenty of complications that can vary from patient to patient.

Adding to the complication that Sjogren's syndrome can sometimes occur with other medical conditions, it becomes a bit tricky to be sure about what exactly is causing your hair to fall.

This makes actually treating hair fall itself even more difficult since certain types of hair loss respond better to some treatments.

4. Vasculitis

Platelets were stimulated by plasma from active AAV patients. The effect of the thrombin-protease-activated receptors (PARs) pathway was evaluated by blocking thrombin or PAR1 antagonists. After platelets were activated by plasma from AAV patients, Ca/Mg-Tyrode's buffer and Mg-EGTA buffer were used to measure complement activation in liquid phase and on the surface of platelets.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of autoimmune diseases that mainly affect small vessels, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The two major antigens in ANCA are myeloperoxidase (MPO) and proteinase 3 (PR3). Cumulative evidence suggests that complement system activation *via* the alternative pathway is indispensable for

the development of AAV. The mechanism of alternative complement pathway activation in AAV is not fully understood, and it is mainly considered to be a downstream effect of neutrophil activation. Increasing studies demonstrate a high prevalence of venous thromboembolic event (VTE) and a hyper coagulant state in AAV patients. In the active stage of AAV, the platelet count is usually elevated. In addition to their classic hemostatic role, platelets are also inflammation protagonists. Platelets and the soluble molecules that they secrete can mediate inflammatory responses and thus contribute to vascular injury. An association between some platelet indices, including platelet counts, mean platelet volume, and disease activity have been reported in AAV and several other autoimmune diseases, such as inflammatory bowel disease, ankylosing spondylitis and rheumatoid arthritis.

Thrombin, the main effector protease in the coagulation cascade, is one of the most potent platelet activators. Activation by thrombin initiates platelet degranulation and secretion, which translocates adhesion receptors to the cell surface, and releases hemostatic and inflammatory agonists/mediators into circulation, then causes surface molecule expression facilitating cellular adhesion. Platelet activation by thrombin depends, at least in part, on signal transduction mediated by a family of G protein-coupled protease-activated receptors (PARs) in many diseases. Our recent study demonstrated that the treatment of C5a-primed neutrophils with ANCA resulted in the release of tissue factor (TF), which subsequently led to thrombin generation.

5. Sarcoidosis

Sarcoidosis is an inflammatory disease that can cause the formation of noncaseating granulomas in the skin or other organs. Cutaneous sarcoidosis involves various types of skin lesions and the cause of the disease is not fully understood, but it may be related to an abnormal immune response to environmental triggers. Platelet-rich plasma (PRP) injections are a treatment that involves injecting a concentration of platelets into the skin or scalp and are often used to improve the appearance of the skin.⁽⁹⁾

It is possible that COVID-19 infections or vaccinations may serve as triggers for the development of skin reactions, including cutaneous sarcoidosis, following PRP injections, but the relationship between COVID-19 and the development of sarcoidal reactions after PRP injections is yet to be elucidated. We report the case of a patient who developed cutaneous sarcoidal lesions at injection sites following PRP therapy after a COVID-19 infection and vaccination, despite having no previous side effects from the treatment.

During a follow-up visit 2 weeks later, her exam was normal. However, 8 weeks after the injections, she developed painless erythematous papules over the lower

eyelids, and neck at the location of previous injections points of PRP. A biopsy of one of the papules, taken from the neck, revealed non necrotizing granulomas, with negative results on PAS stain, consistent with cutaneous sarcoidosis. Further testing, including a chest X-ray, a CT scan, and pulmonary studies, were all negative for systemic sarcoidosis. The patient was treated with topical pimecrolimus and oral combination of desloratadine and betamethasone for 2 weeks, which improved her condition. The lesions recurred once the treatment was discontinued. A trial of oral doxycycline 100 mg once daily for 1 month showed no benefit. She was then started on hydroxychloroquine 200 mg BID for 6 months, which led to partial resolution and no new lesions 3 months after drug discontinuation. (5)

It is worth mentioning that the patient had previously received four other PRP sessions since 2018 using the same kit, needles, syringes, and injection technique without any complications. However, she did receive the COVID-19 vaccine in May 2021 and the booster in June 2021, 6 months prior to the appearance of the lesions. She also had a COVID-19 infection in December 2020, confirmed by PCR. During the time between the vaccine administration and the development of her lesions, she could have also caught an undocumented COVID infection from her children (who were sick at the time). It is also relevant to mention that the patient had scars from a previous breast augmentation surgery which were examined and did not reveal any suspicious dermatological disorder. We would like to note that the patient's consent to publication of information and images was taken.

6. Crystalline Arthropathies

Rheumatic diseases (RD) are a spectrum of autoimmune conditions that can cause damage to the musculoskeletal system as well as other vital organs, such as the heart, lungs,

kidneys, and central nervous system. Rheumatic diseases are becoming increasingly common due to longer life expectancy and an aging general population, with a prevalence of about 1 in 4 adults in the United States. The Center for Disease Control has recently predicted that their prevalence will likely continue to increase by 49% by 2040.

There have been significant advances in the study and understanding of pathophysiologic mechanisms and therapeutic interventions involving RD over the last few years. Through the growth of the medical armamentarium involving the use of glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) and newer synthesized biological immunomodulating agents, physicians are now able to positively impact the prognosis, quality of life, and functional capacity of these patients. However, despite the advancement of available therapies, some limitations persist, and many patients are often not suitable for long-term management due to lack of lasting efficacy, side effects, cost, and lack of insurance coverage, all of which

can contribute to discontinuation and suboptimal outcomes.(17)

One potential treatment option that has not been well investigated or FDA-approved in RD is the use of platelet-rich plasma (PRP). PRP is an autologous blood product composed of a processed liquid fraction of peripheral blood with a platelet concentration above the baseline. The exact mechanisms by which PRP exerts its clinical benefits are unclear. It is believed to stimulate the expression of anti-inflammatory molecules in high concentrations. These molecules include growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), epidermal growth factor (EGF), fibroblast growth factor (FGF), and platelet-derived growth factor. (18)

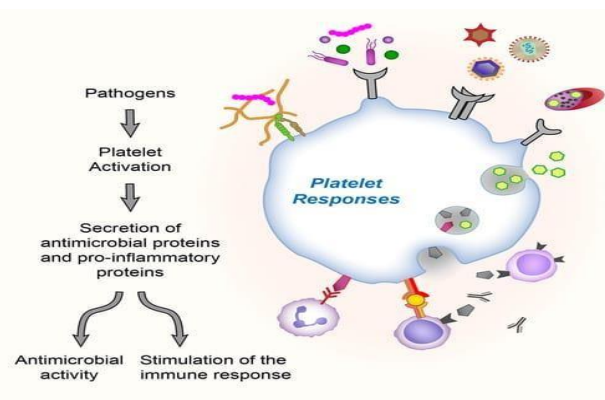


Fig.3 Crystalline Arthropathies

Significant research has been conducted to determine the most effective composition and PRP concentration needed to achieve the greatest reduction in the inflammatory response. The impact of the final PRP volume, platelet, EGF, VEGF, leukocyte concentrations, and platelet activation markers has been extensively studied in the literature. However, many studies still use different preparations, which may influence results.(19,20)

Recently, PRP has shown promising results as an immunomodulatory agent in cell and animal models. Given these findings, PRP has been investigated in several areas of the medical field, including regenerative medicine in orthopedic surgery, sports medicine, dentistry, cardiac surgery, pediatric surgery, gynecology, urology, plastic surgery, ophthalmology, and dermatology. Nevertheless, the results of randomized clinical trials have been mixed. This retrospective narrative review aims to summarize results and provide a state-of-the-art analysis of the clinical benefits of PRP use and its possible side effects in a variety of RD.

Conclusion

The best evidence for an impact occurs at the one- to two-month follow-up. Low- and moderate-quality data indicate that PRP helps patients with hip OA perform better and experience less pain when compared to baseline. Low-quality evidence attributes a greater pain reduction with a total injected dose of PRP~15 mL compared with 15 mL, or using a leukocyte-poor PRP preparation compared with

leukocyte-rich PRP. Moderate-quality evidence suggests that a larger reduction in pain is achieved with a single PRP injection compared with multiple injections. Lastly, PRP injections did not have any long-term negative effects. To determine whether PRP injections are more beneficial for patients with hip OA than other currently available nonsurgical therapy options, large-scale, methodologically sound trials with gold standard control groups should be carried out.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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