IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Platelet Rich Plasma Therapy In Musculoskeletal Injury And Sports Medicine.

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1. INTRODUCTION -

Platelet-Rich Plasma (PRP) is an advanced therapeutic solution derived from a patient's own blood. This autologous preparation involves concentrating platelets above baseline levels within a small volume of plasma. PRP is typically produced through a two-stage centrifugation process. In the first centrifugation phase, blood components are separated based on density; the red blood cells settle at the bottom while the buffy coat, containing platelets, white blood cells, and clotting factors, forms a distinct layer (Figure 1).[1]

During the second centrifugation phase, the PRP fraction is isolated from the platelet-poor plasma (PPP), ensuring a high concentration of platelets. For effective PRP preparations, various single-step methods are also available. While normal platelet counts in human blood range from 150,000 to 300,000 platelets per microliter, the working definition of PRP is a concentration of approximately 1,000,000 platelets per microliter in a 5-mL sample of plasma. This high concentration is essential for maximizing the healing potential of PRP therapy, which utilizes the growth factors released by activated platelets to enhance the body's natural healing processes.[1]

The theory behind Platelet-Rich Plasma (PRP) therapy is grounded in the belief that concentrating platelets at the site of injury can significantly enhance the body's natural healing processes. When activated, platelets release a variety of growth and differentiation factors that are essential for tissue repair and regeneration. Among the key bioactive factors released are Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor (TGF-β), Fibroblast Growth Factor (FGF), Insulin-like Growth Factor (IGF), Vascular Endothelial Growth Factor
(VEGF), Hepatocyte Growth Factor (HGF), Epidermal Growth Factor (EGF), and Platelet Factor 4 (PF4). [1]

These factors are pivotal in regulating crucial cellular functions such as cell division, metabolism, chemotaxis (the directed movement of cells toward chemical signals), and mitogenesis (the process of cell division). For instance, PDGF and TGF-β stimulate the proliferation of cells necessary for tissue formation, while VEGF promotes angiogenesis, ensuring an adequate blood supply to the healing tissues. This coordinated release of growth factors attracts various cell types, including fibroblasts and endothelial cells, thereby creating a supportive environment for repair. [1]

PRP therapy leverages concentrated growth factors to accelerate healing, reduce inflammation, and alleviate pain, making it an effective treatment for various conditions. These include orthopaedic injuries, tendonitis, and aesthetic concerns such as skin rejuvenation and hair restoration. As PRP therapy gains traction across diverse medical fields, ongoing research is focused on optimizing its applications. This research seeks to enhance recovery by harnessing the body's innate healing mechanisms, ultimately improving patient outcomes. With its promising benefits, PRP therapy is increasingly recognized as a versatile and effective option in both therapeutic and cosmetic practices, reflecting its growing acceptance and application in modern medicine.[1]

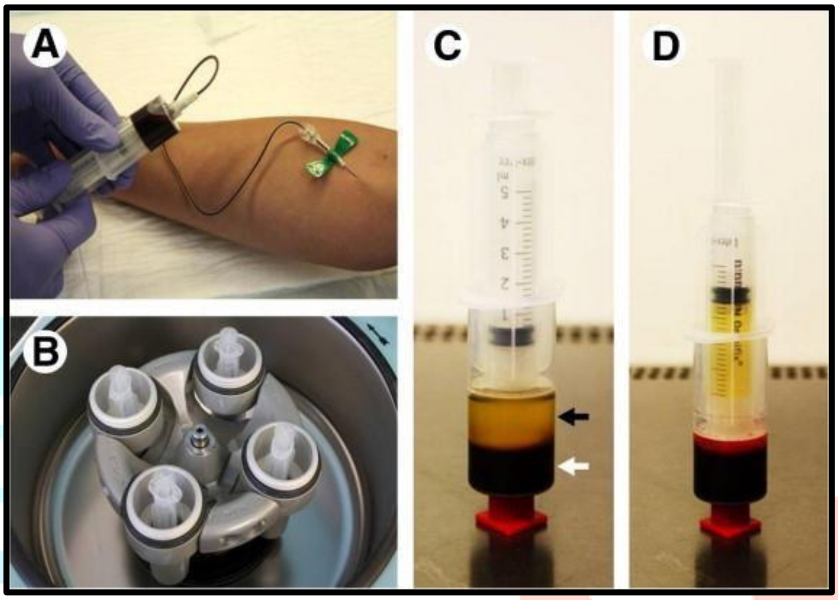

Figure 1: A single-step centrifugation technique for the preparation of autologous serum. (A) Autologous blood aspiration by cubital vein puncture using a twin syringe method. (B) After balancing, one or more syringes can be put in the appropriate buckets of a tabletop centrifuge and spun. (C) After that, the red blood cell fraction (white arrow) is neatly separated from the serum fraction (black arrow), which contains the platelets, white blood cells, and clotting factors (buffy coat). (D) The serum fraction may now be simply and sterilely separated from the red blood cell fraction for use in other procedures by unscrewing the stamp on the second syringe of the closed system.[1]

Platelet-Rich Plasma (PRP) is also known as Platelet-Leukocyte-Rich Plasma (PRP-rich plasma), a term that more accurately reflects its composition when used in clinical contexts. Additionally, it can be referred to as "platelet-rich concentrate" or "platelet concentrate." However, these terms typically describe a platelet pellet that contains minimal plasma.[1]

When PRP is activated with substances like thrombin or calcium, it transforms into a coagulated form known as PRP "gel." This gel is particularly useful in various medical applications, providing a scaffold that supports tissue regeneration and enhances healing. The ability to create a gel-like consistency adds versatility to PRP therapies, allowing it to be utilized in both aesthetic and surgical procedures. By leveraging the unique properties of PRP, clinicians can effectively promote healing and tissue repair in a range of clinical scenarios.[1]

1.1. BACKGROUND -

Platelet-rich plasma (PRP) is an autologous blood product that is highly concentrated in growth factors and cytokines, which play crucial roles in tissue healing and immunomodulation. This therapy involves a simple and minimally invasive procedure that poses no risk of immunological reactions, making it a safe and cost-effective option for patients. [2]

Current evidence supports the use of PRP therapy for a variety of orthopaedic conditions, showcasing its efficacy compared to traditional treatments such as hyaluronic acid and corticosteroids. Clinical studies have demonstrated that PRP can provide superior benefits, leading to reduced inflammation and discomfort, improved joint function, and potential cartilage regeneration. [2]

The growth factors present in PRP stimulate cellular processes essential for healing, such as angiogenesis, collagen synthesis, and the recruitment of reparative cells. As a result, PRP therapy has gained popularity in treating conditions like osteoarthritis, tendon injuries, and ligament sprains. With ongoing research, the understanding of PRP's therapeutic potential continues to expand, reinforcing its role as a valuable tool in orthopaedic medicine and regenerative therapies, enhancing patient outcomes and quality of life. [2]

In the course of their regular work, our staff treats patients with haemophilia as well as those suffering from various musculoskeletal disorders. Among these conditions, the use of plateletrich plasma (PRP) therapy has shown promising results, particularly in the treatment of chronic synovitis. Patients have reported fewer episodes of bleeding, reduced discomfort, and decreased joint swelling, highlighting PRP's potential to enhance healing and improve overall joint function. [2]

Even though the process is usually safe, it's crucial to be prepared for any difficulties. Problems including abscesses, skin necrosis, or septic arthritis might happen after intramuscular or intraarticular injections, however they are uncommon. A number of things, such as iatrogenic inoculation or using the wrong technique while injecting, might cause these issues.[2]

Careful patient selection and thorough adherence to aseptic practices are necessary to reduce these hazards. After an injection, our staff closely monitors patients to quickly manage any side effects. To enhance the therapeutic benefits of PRP while minimizing potential side effects, our focus prioritizes safety and efficacy. This approach aims to improve patient outcomes in both musculoskeletal treatments and hemophilia therapy, ensuring optimal results for all patients.[2] **1.2. AIMS TO ACHIVE -**

PRP injections are being tested by researchers for a variety of purposes. Some instances of these are:

- **Tendon Damage: -**

Tendons are strong, thick strands of tissue connecting muscles to bones, and they often heal slowly after injury. Medical professionals use platelet-rich plasma (PRP) injections to effectively address persistent tendon issues. Conditions such as jumper's knee, which affects the patellar tendon, tennis elbow, and Achilles tendonitis can benefit from PRP therapy. By delivering concentrated growth factors directly to the injured area, PRP promotes healing, reduces inflammation, and alleviates pain, making it a valuable treatment option for individuals suffering from chronic tendon injuries. This approach enhances recovery and improves overall function.[3]

- **Acute Wounds: -**

PRP injections are frequently used by medical professionals to treat acute sports injuries, including knee sprains and strained hamstring muscles. This therapy delivers concentrated growth factors directly to the injury site, promoting healing and reducing inflammation. By enhancing the body's natural recovery processes, PRP helps athletes regain strength and function more quickly after injury, enabling a faster return to their sports activities and overall performance.[3]

- **After Surgery: -**

PRP injections are becoming an integral part of postoperative care in orthopaedic surgery, especially following procedures to repair damaged ligaments, such as the anterior cruciate ligament (ACL), or tendons like the rotator cuff in the shoulder. These injections deliver a concentrated mixture of growth factors directly to the surgical site, promoting faster healing and reducing postoperative pain and inflammation. By stimulating the body's natural healing processes, PRP therapy enhances tissue regeneration and accelerates recovery.[3]

This innovative approach not only aims to improve surgical outcomes but also facilitates a quicker return to normal function and activity levels for patients. As a result, individuals can resume their daily activities and sports more rapidly, significantly enhancing their quality of life. Ongoing research continues to explore the full potential of PRP therapy in various orthopaedic applications, further solidifying its role as a valuable tool in modern surgical practice.[3]

1.3. APPLICATION -

- **Chronic Tendinopathies Can Manifest in Various Areas, Including:**
  - Elbow (lateral and medial epicondylitis)
  - Shoulder (positive outcomes observed with rotator cuff tendinosis in patients without full-thickness tears or retraction)
  - Hip (notably in the gluteal, adductor, and proximal hamstring regions)
  - Knee (patellar tendon issues)
  - Foot/ankle (concerns such as Achilles tendinopathy, peroneal tendon issues, and plantar fasciitis) [4]

- **Chronic Pain and Osteoarthritis:**
  - Knee (excellent outcomes if performed comprehensively, including treating intra- and periarticular structures; lower grades of arthritis without major deformity are most likely to respond; often of value after treatment with steroids or Visco supplementation no longer helps)
  - Ankle and foot
  - Shoulder (glenohumeral and acromioclavicular) Hip[4]

- **Chronic Ligamentous Injury and Pain:**
  - Ankle
  - Knee
  - Hip
  - Sacroiliac joint[4]

- **Muscle:**
  - Subacute and chronic symptomatic intrasubstance muscle tears.[4]

1.4. ADVERSE REACTIONS OF PLATELET-RICH PLASMA THERAPY -

- **Anguish in the Affected Area:**

After receiving PRP treatment, some patients experience sharp pain or discomfort at the injection site. This discomfort can sometimes radiate deep into the affected area, impacting the bone or muscle. While these sensations are typically temporary, their intensity and duration can vary among individuals, necessitating monitoring and potential follow-up care to ensure proper recovery.[5]

- **Virus Infection:**

Despite strict sterilization protocols being followed for every PRP treatment, there remains a small risk of infection at the injection site. While these occurrences are rare, they can arise from various factors, including the body's response to the procedure. It's essential for medical professionals to closely monitor patients post-injection and educate them about potential signs of infection, ensuring timely intervention to safeguard patient health and promote effective recovery. [5]

- **No Change in The Affected Area:**

While PRP injections can be beneficial, not every athlete experiences positive results. Ongoing research in this area aims to clarify the factors influencing effectiveness. In some cases, despite a period of rest following PRP therapy, the original pain and discomfort may persist or even worsen. This variability underscores the importance of individualized treatment approaches and continued exploration in sports medicine to better understand the outcomes of PRP therapy.[5]

- **Hypersensitive Reactions:**

While rare, some individuals may experience a negative reaction to PRP therapy, where their body seemingly rejects its own serum. This unexpected response can lead to complications or a lack of effectiveness in treatment. Understanding the underlying reasons for these reactions is essential, as further research is needed to identify risk factors and mechanisms involved. Such insights could help improve patient selection and optimize the use of PRP therapy in
clinical practice. [5]

- **Clot of Blood:**

A blood clot typically forms following an injury to the blood vessel lining, such as from a cut. During a PRP injection, there is a small risk of damaging an artery or vein, as the procedure involves a needle guided by ultrasonography. If a blood clot does occur, it is managed in the same manner as any other clot, ensuring appropriate care for the patient.[5]

- **Skin Discolorations:**

Occasionally, the area around a PRP injection can seem bruised. Given your history of bruises, this could be typical. On the other hand, get in touch with your doctor right away if the bruise is really deep and black or if you just don't bruise readily.[5]

2. MECHANISM OF ACTION -

Thrombocytes, commonly referred to as platelets, are small, nucleated cells produced in the bone marrow, with a diameter of approximately 1.5–3 µm. They are the smallest cells in the blood and play a pivotal role in various physiological processes. A normal platelet count ranges from 150,000 to 450,000 per microliter, and any significant deviation from this range can indicate underlying health issues.[6]

Platelets are best known for their critical function in haemostasis, the process of blood clotting. When vascular injury occurs, platelets quickly adhere to the damaged site, undergo activation, and aggregate to form a stable clot. This rapid response not only helps to prevent excessive blood loss but also initiates the healing process by providing a scaffold for tissue repair. Upon activation, platelets release numerous coagulation-promoting substances from their granules, including serotonin, calcium ions, and various clotting factors. These substances enhance platelet aggregation and amplify the clotting cascade, ensuring effective haemostasis. [6]

Recent research has illuminated the multifaceted roles of platelets beyond haemostasis. They serve as a substantial source of growth factors (GFs) and cytokines, which play vital roles in tissue repair and regeneration. These bioactive molecules influence several processes, including angiogenesis (the formation of new blood vessels), inflammation, and stem cell migration. Additionally, platelets are involved in cell proliferation, differentiation, and tissue morphogenesis. Their ability to release these factors at the injury site underscores their importance in orchestrating a coordinated healing response.[6]

Moreover, platelets act as chemical messengers that facilitate complex interactions between different cell types, including connective tissue cells, epithelial cells, and immune cells. This dynamic interplay is crucial for effective tissue healing, as platelets help recruit various cell types to the injury site, thereby enhancing the repair process. Their role in chemotaxis—the movement of cells in response to chemical signals—further emphasizes their importance in the healing cascade.[6]

In summary, platelets are not merely components of the clotting system; they are integral players in the complex network of tissue healing. Their rich composition of growth factors and cytokines enables them to significantly contribute to both immediate protective responses and long-term repair mechanisms. As our understanding of platelet biology continues to evolve, it becomes increasingly clear that these small cells are vital for maintaining homeostasis and facilitating the body's ability to heal and regenerate effectively. Their multifunctional role positions them as key targets for therapeutic interventions in various medical conditions, especially in regenerative medicine and orthopaedic therapies.[6]

3. BEST TIME FOR PRP ADMINISTRATION -

At the moment, we use PRP on patients who are functionally impaired, have a pain score that averages more than 4 on a 0–10 visual analog scale, and have not responded to a thorough trial (3-6 months, usually closer to the 6-month duration) of standard management and rehabilitation for sports injuries. The athlete must also be given enough time to rest during the first uncomfortable post-procedure phase. We handle each patient individually; for additional information, see the activity progression below. Our program averages a return to sports at roughly 4 weeks for individuals in these chronic situations, however it might vary from 3 weeks to 3 months. The following are examples of variables: the degree and kind of sports activity, the severity of the injury, the duration of the symptoms, the type and quantity of injections administered, and the other medical comorbidities or the other orthopaedic comorbidities. Our suggested administration timeframe for acute injuries is seven to ten days. This timeline is based on anecdotal evidence and is corroborated by Chan et al.'s research on an animal model of patellar tendon damage.[4]

Using PRP treatment on day 7 of the injury showing better benefits than day 3 of the injury. In acute situations, a person's return to sport is quite unpredictable and is handled case by case based on the pathology, severity of the injury, athlete's level, and availability of training facilities and physical treatment. The athlete's ability to tolerate discomfort will determine how far they may advance through the phases of recovery and sports-specific training. Reducing an injury's healing period by a minimum of two weeks is the aim. Since a consistent method has not yet been created and individuals in the subacute period are examined individually, the indications for these patients are not covered here.[4]

4. RECOMMENDED AMOUNT OF PRP INJECTIONS -

In our practice, we typically begin with a single PRP injection for treatment. Each injection is performed under the careful supervision of musculoskeletal ultrasonography, ensuring precision and safety throughout the procedure. Following the injection, we provide patients with tailored exercise regimens and specific criteria for progression to aid in their recovery. [4]

Patients are scheduled to return for a follow-up appointment in approximately six to eight weeks. During this visit, we assess their progress. If a patient reports an improvement of 80% or more, we refrain from administering additional injections and continue to support their activity progression. This approach emphasizes the importance of individual recovery and the effectiveness of the initial treatment. [4]

Conversely, if a patient desires further improvement and reports less than 80% progress, we may consider a second injection. Importantly, the decision to pursue additional treatment is made collaboratively, giving each patient complete discretion over their care plan. This patientcentered approach fosters trust and empowers individuals to take an active role in their recovery journey, ultimately enhancing their overall treatment experience and outcomes.[4]

5. ACTIVITIES TO ENCOURAGE OR AVOID DURING BREAKS -

Activity progression and post-procedure discomfort are shown to be varied. The postoperative discomfort usually subsides in a span of two to ten days. We immediately begin range of motion as soon as it is tolerated. Within three to seven days, on average, we have the patient advance to light aerobic activity as tolerated. In three to four weeks, the patient advances to strengthening and sports-specific training; however, it should be noted that this time frame varies greatly among athletes who compete in different sports.[4]

6. EFFECT OF NSAIDs ON PRP THERAPY -

Following a procedure, we encourage patients to refrain from using NSAIDs for at least 10 days, and ideally 3-6 weeks. NSAIDs are withheld for empirical, but unverifiable, reasons. By changing the cellular environment required for the initial (inflammatory) stage of the healing cascade, NSAIDs impede the prostaglandin pathway and may lessen the positive effects triggered by the release of growth factors from the supplied platelets.[4]

According to theory, using NSAIDS might prevent, slow down, or possibly cause fibrosis in the tissue. Nevertheless, there is currently no human clinical data in support of this treatment. Patients on systemic steroids or immunosuppressive medications are often not candidates for PRP therapy, however this may need to be evaluated on a case-by-case basis. Low-dose aspirin administered for cardiac prevention is not withheld.[4]

7. CLASSIFICATION SYSTEM -

Different writers have suggested categorization schemes for the different kinds of PRP. Dohan Ehrenfest et al provided a categorization scheme (Table 1) that was predicated on the subsequent two elements:

Cell content, particularly in regard to white blood cells, and a architecture of fibrin. These characteristics allow for the classification of PRP into four distinct categories. Pure PRP (P-PRP), which does not have a low-density fibrin network and leukocytes.
The quantities of leukocyte-rich PRP (L-PRP) are higher than white blood cells together with a high platelet content, features a low-density fibrin network as well. Next, pure plateletrich fibrin has a high fibrin density but lacks leukocytes. A high-density fibrin network enriched with platelets and leukocytes is known as leukocyte- and platelet-rich fibrin (LPRF). This composition unites elevated leukocyte concentrations with a robust fibrin web, promoting enhanced healing. LPRF is particularly beneficial in regenerative medicine, where its injectable applications are commonly used in orthopaedic and sports medicine. In contrast, preparations with a low-density fibrin network offer versatility for various treatments but lack the same growth factor concentration. High-density fibrin preparations, including LPRF and pure platelet-rich fibrin (PPRF), facilitate the formation of a stable clot that integrates growth factors into its matrix architecture, supporting tissue regeneration and repair.[7]

Type of Platelet-Rich Plasma	Presence of Leukocytes?	Fibrin Architecture
Pure platelet-rich plasma (P-PRP)	No	Low density
Leukocyte- and platelet-rich plasmas (L-PRP)	Yes	Low density
Pure platelet-rich fibrin (P-PRF)	No	High density
Leukocyte- and platelet-rich plasma (L-PRF)	Yes	High density

Table 1 – Classification of PRP Types[7]

The three-factor-based PAW categorization (Table 2) was proposed by DeLong et al. The activation system (A), the quantity of platelets (P), and the presence or absence of white blood cells (W) are the three parts of this system. There are four categories of platelet concentration, designated P1 through P4. P1 preparations have concentrations that are at or below baseline levels; P2 preparations have concentrations between baseline and 750,000 platelets/mL; P3 preparations have concentrations between 750,000 and 1,250,000 platelets/mL; and P4 preparations have concentrations beyond 1,250,000 platelets/mL.[7]

An x indicates that an external activator is being used. Lastly, the leukocyte concentration is categorized as being either higher than the baseline value (A) or lower than it (B). Similar groupings exist for the neutrophil concentration: above (α) or below (β) whole blood values.[7]

Even if there isn't a single categorization system that is consistently applied and the terminology for platelets remains inconsistent, it is imperative that medical professionals understand the composition of the PRP they are administering to their patients. The best kind and time of PRP injections for each clinical condition won't be identified till after that.[7]

Elements of Classification System	Representation	Definition
Platelet concentration	P1	Platelet concentration ≤ baseline concentration
	P2	Platelet concentration from baseline to 750,000 platelets/μL
	P3	Platelet concentration from 750,000-1,250,000 platelets/μL
	P4	Platelet concentration > 1,250,000 platelets/μL
Activator	*x*	Exogenous activator used
White blood cell presence	A	Leukocyte concentration above baseline level
	B	Leukocyte concentration below baseline level
	α	Neutrophil concentration above baseline level
	β	Neutrophil concentration below baseline level

Table 2 – PAW Classification of Platelet Rich Plasma[7]

8. ACTIVATION METHOD, CARRIERS, AND ADDITIVES -

PRP studies and clinical applications involve a variety of activators and carriers with varying therapeutic effects. There has been discussion on the best activation technique to employ in clinical practice as well as the need of using PRP activation in any particular way. The activation route involves the release of alpha granules by platelets. This process generally happens when collagen and platelets come into touch, most often as a result of vascular damage. PRP can be used in therapeutic settings to manipulate the timing of growth-factor release by taking advantage of this innate mechanism.[7]

The goal of exogenous PRP activation to produce PRF before to injection is to guarantee the prompt availability of growth factors. A clot produced via exogenous activation can then be implanted in the intended site. Growth factors are incorporated in a structural framework that is provided by the fibrin matrix of PRF. This makes it possible to provide more individualized care and is frequently applied when using PRP during surgery. One way for activating PRP has been the use of bovine thrombin. An other choice is autologous thrombin, which can be used with or without calcium chloride. These substances work as a catalyst to change fibrinogen into fibrin. There are certain drawbacks to using cow thrombin, though. This has been linked to immunological response, thrombosis, and bleeding. One mild exogenous activator of PRP that can be utilized to induce the release of PDGF-AB is calcium chloride. However, because calcium chloride has a low pH of 6.3. Patients may feel more discomfort. Endogenous activation depends on PRP being exposed to collagen or coagulation factors that are expressed upon injection. Harrison and colleagues examined the daily concentrations of TGF-B1, PDGFAB, and VEGF over a period of seven days after to PRP activation using either collagen or thrombin. Growth factors were released immediately upon activation with thrombin, but over the course of seven days, a sustained-release pattern of growth factors was seen following collagen activation. [7]

Patients with long-term degenerative knee alterations received PRP activated with 10% calcium chloride, according to Filardo et al. The IKDC scores showed a substantial increase from 47% of baseline to 67% at 1 year (P o 0.0005) and 59% at 2 years (P 0.04). PRP polymerized with thrombin in conjunction with microfracture was superior than unactivated PRP with microfracture or microfracture by itself, according to a sheep investigation on osteochondral lesions. Excellent defect fill and mean stiffness comparable to normal cartilage were the outcomes of treatment with PRP polymerized with thrombin. The biomechanical stiffness was considerably poorer (P ¼ 0.0007) for both the microfracture group and the microfracture and inactivated PRP 10 D.A. Lansdown, L.A. Fortier group, and the defect fill was lower for inactivated PRP. Activated PRP in gel form may serve as a scaffold for cartilage healing and lower the danger of growth factor diffusion into the knee when treating localized cartilage lesions. [7]

Lastly, it's critical to take into account an additive's pH and how it affects platelet activity. Wahlström et al.'s research from showed that the osteoblastic response to platelets was pHdependent, with an acidic environment releasing more powerful growth factors. When thinking about using local anaesthetics, it's also critical to understand the pH-based variation in platelet activity. Borg and associates assessed platelet function following tocainide, lidocaine, and bupivacaine incubation. The local anaesthetics' impact on platelet function varied with time, with lidocaine having the most potential to reduce platelet aggregation. These results were validated by Porter et al., who reported that ropivacaine markedly impairs normal platelet coagulation and aggregation. For these reasons, before administering local anaesthetics in combination with PRP, it is important to thoroughly examine their requirement.[7]

9. PREPARATION -

- **Initial Preparation:**

The first step in making PRP is taking the patient's peripheral blood. Red blood cells make up 93% of peripheral blood, platelets make up 6%, and leukocytes make up 1%. Blood collection requires caution since some aspects of the procedure might affect the quality of the finished PRP product. For instance, using a tiny needle to take blood may cause the platelets to activate too soon. A 21-gauge or larger needle should be used to obtain blood for the production of PRP. Blood should be aspirated gently since the pace at which it is taken may also affect the quality of the platelets.[7]

Once a patient's blood is extracted, it passes through a cell components and liquid using a centrifugation method. This spinning process's objective is to focus platelets and reduce the erythrocytes' relative bulk. The The initial spin is carried out at about 900 g. The objective behind separating platelets from red and white blood is the purpose of this stage. cells. After then, a second spin might or might not be used. This At 1500 g, a second, quicker spin is carried out, serving to generate a buffy covering and push the platelets even farther into the in the same stratum as leukocytes. [7]

The two fundamental techniques for preparing PRP are buffy coat-based and plasma-based. There is only one slow, brief spin (five minutes) in plasma-based preparations; there isn't a second spin. This procedure reduces the amount of leukocytes and erythrocytes in the preparation while isolating platelets and plasma. Using this approach, the ultimate platelet volume is often two to three times higher than the starting concentrations. An alternative preparation might be made using buffy coat. In order to isolate the most platelets possible, this approach uses a second, high-spin speed centrifugation that lasts for ten to fifteen minutes. Leukocytes and erythrocytes are still present in the preparation, but the platelet concentrations are 3–8 times greater than those obtained using a plasma–based preparation.[7]

The materials utilized to prepare PRP have an impact on the finished result as well. It has been demonstrated that polypropylene tubes work best for preparing and storing platelets. Other materials used to make the tubes, such as glass and polystyrene, might cause changes in platelet shape or early platelet activation. For these reasons, while developing a PRP protocol, researchers must take notice of these parameters, and doctors should adhere to these guidelines when making PRP.[7]

To prepare PRP, a variety of commercial technologies are available. Castillo et al. examined three distinct systems (MTF Cascade, Arteriocyte Magellan, and Biomet GPS III) and demonstrated that the concentration of leukocytes and growth factors varied amongst the PRP preparations. With a mean 2.18-fold increase in platelet concentration above the baseline level, there were no statistically significant changes in platelet concentration. The leukocyte concentration decreased six times with the Cascade system, but it increased two times with the GPS III and five times with the Magellan systems. Transforming growth factor-beta 1 (TGFβ1) concentrations from each of the three systems' products did not differ significantly.[7]

The quantities of VEGF in the Cascade PRP were notably lower than those of the GPS III PRP (P ¼ 0.004). Additionally, the Cascade PRP had considerably lower amounts of platelet-derived growth factor-AB (PDGF-AB) (P ¼ 0.006) and PDGFBB (P ¼ 0.008) much lower than the amounts found in the Magellan PRP.[7]

PRP generated by seven distinct commercial systems—JP200, GLO PRP, Magellan Autologous Platelet Separator System, KYOCERA Medical PRP Kit, SELPHYL, MyCells, and Dr. Shin's THROMBO KIT—was compared by Kushida et al. With the Magellan system, the platelet concentration increased nine times above the baseline; with the SELPHYL system, it was 0.52 times higher than the baseline. All six systems produced platelet concentrations that were at least three times greater than the baseline, with the exception of the SELPHYL system, which produced low platelet concentration. Five systems (JP200, GLO PRP, Magellan, KYOCERA, and MyCells) generated PRP with PDGF-AB concentrations that were not statistically different from one another, however two systems (SELPHYL and Dr. Shin) produced PRP that had much less PDGF-AB. In conclusion, the price range for these systems was US$50 (JP200) to US$500 (Magellan). The sole system used in each of these investigations was the Magellan PRP system, and in Castillo et al., the platelet concentration was 2.8 times higher than baseline values, but in Kushida et al., it was 9 times higher. These investigations show how PRP varies depending on the method employed and emphasize how crucial it is to comprehend the possible therapeutic impacts of the different components, such as the concentration of platelets and leukocytes in PRP.[7]

The concentration and quality of a patient's platelets can be affected by a number of patientspecific variables that can be changed. In comparison to fasting, a high-fat meal has been demonstrated to raise peripheral platelet concentration in healthy participants. Platelet concentration and function are similarly influenced by circadian rhythms; platelet concentrations rise in the afternoon and platelet activation falls from midday to midnight. It is important to take into account each of these elements when producing PRP for clinical or research use.[7]

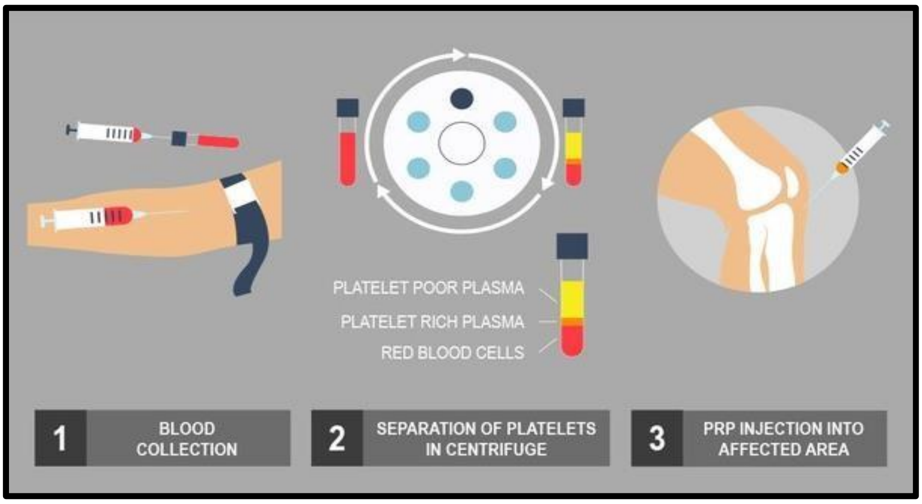

Figure 2: PRP Procedure[8]

10 . TYPES OF CONCENTRATIONS -

10.1. PLATELET CONCENTRATION -

Regarding the makeup of their blood, patients differ greatly from one another as well. A typical platelet concentration in the bloodstream is between 150,000 and 350,000 platelets/mL. It was shown by Andrade et al. that there was a positive correlation (r ¼ 0.535) between the initial platelet concentration in whole blood and the end platelet concentration in PRP. Six athletes underwent platelet-rich fibrin matrices augmentation for Achilles tendon repair, and Sánchez et al.'s evaluation revealed a significant positive correlation between the concentration of platelets and the levels of PDGF-AB, TGF-β1, VEGF, hepatocyte growth factor, and epidermal growth factor.[7]

However, there is a spectrum where PRP can work, and too low or too high platelet concentrations might work poorly or have unfavorable clinical outcomes.[7]

Weibrich et al. provided evidence about the impact of platelet concentration on the result. A platelet concentration of 1,000,000 platelets/mL was observed to favorably correlate with bone regeneration after 4 weeks in a rabbit investigation investigating the effect of PRP in bone regeneration. When compared to a control group, using PRP at a lower concentration (0.5–1.5 times the whole-blood platelet concentration) did not improve bone repair. On the other hand, bone repair was inhibited by PRP therapy with platelet concentrations 6–11 times greater than baseline levels. Numerous clinical and preclinical investigations suggest the effectiveness of platelet concentrations above baseline up to 750,000 platelets/mL (1-4 baseline) in tissue regeneration.[7]

The amount of time it took to resume sports following Achilles tendon repair augmentation using platelet-rich plasma (PRP) that included three times the initial blood concentrations was reported by Sánchez et al. According to this study, athletes treated with PRP-augmented repair were able to return to sport 7 weeks earlier than those treated with tendon repair alone (14 weeks in the PRP group vs. 21 weeks in the control group; P ¼ 0.004). They also recovered their range of motion earlier (7 weeks in the PRP group vs. 11 weeks in the control group; P ¼ 0.025).[7]

In an equestrian study by Torricelli et al., the optimal platelet concentration for resuming competition in racing horses after musculoskeletal injuries was found to be 750,000 platelets/mL, which represents a mean of 5.4 times the baseline concentration. Horses treated with PRP at or above this concentration returned to competition in an average of 2.8 months. In contrast, those receiving lower concentrations took longer to recover, with a statistically significant difference noted ($P = 0.049$). This highlights the importance of platelet concentration in the recovery process.[7]

High platelet concentrations are typically defined as 4-6 times the baseline, ranging from 750,000 to 1,800,000 platelets/mL. In a study by Hee et al., patients undergoing lumbar interbody fusions with high-concentration PRP—specifically 4.89 times the baseline platelet concentration—demonstrated significantly improved bone healing compared to a historical control group who did not receive PRP treatment. This suggests that using high-concentration
PRP can enhance the healing process following spinal fusion surgeries.[7]

For single-level fusions, the fusion rate was 100%, while for multilayer fusions, it was 90%. The rate of pseudoarthrosis was 4% in the historical control group, but the authors found none. In meniscal tears, tendon injuries, and other locations with inadequate vascularity, increased angiogenesis aids in the healing process. PRP's angiogenic effects peaked at this platelet concentration, with diminishing efficacy at both lower and higher platelet concentrations, as determined by stimulating the proliferation of human umbilical vein endothelial cells. A platelet concentration of 1,500,000 platelets/mL produced the greatest results in an in vitro research on endothelial cell growth. These studies highlight how platelet concentration affects PRP's therapeutic impact. This recommends that for therapeutic reasons and in research projects, platelet concentration should be recorded and modified according to the clinical indication.[7]

10.2. LEUKOCYTE CONCENTRATION -

Leukocytes are essential to a healthy immune system and are present in peripheral blood circulation. Neutrophils, eosinophils, basophils, lymphocytes, and monocytes are all included in the category of leukocytes. Leukocytes attach to active platelets for transmigration, and platelets facilitate leukocyte recruitment to inflammatory regions, among other intricate interactions between platelets and leukocytes. The function of platelet-rich plasma (PRP) is significantly impacted by the inclusion or exclusion of leukocytes in the formulation. Leukocytes may be beneficial or detrimental to therapy, depending on the goal and injection site. Elevations in leukocyte concentrations are associated with rises in inflammatory cytokine concentrations, including TNF-, IL-6, IL-8, and interleukin-1β (IL-1β).[7]

If L-PRP is injected to treat an acute muscular injury, there is a danger of muscle damage, mostly because of neutrophils. Neutrophils aid in the breakdown of muscle damage byproducts and are present soon after muscle injury. However, these cells' activities may potentially directly lyse muscle cell membranes and reduce muscular contractility.[7]

When compared to leukocyte-poor PRP, Dragoo et al. showed a greater inflammatory response following the injection of rabbit tendons with L-PRP. Five days following injection, the tendon structure in the L-PRP group was noticeably more disturbed than in the leukocyte-poor PRP group. Furthermore, at 5 days, the L-PRP group showed noticeably greater fibrosis than the leukocyte-poor PRP group. Nevertheless, after 14 days, there were no discernible variations between the groups, since every tendon had signs of heightened cellularity.[7]

The effects of PRP on the repair of horse flexor tendons were studied by McCarrel et al. at different leukocyte concentrations. Elevated levels of leukocytes in PRP were linked to elevated expression of TNF-α and IL-1β, which are present in tendinopathy but not in healthy tendons. These results imply that utilizing PRP to treat tendon-based diseases may not benefit from the inclusion of leukocytes.[7]

When injected intra-articularly, leukocytes may change the effects of platelet-rich plasma. Filardo et al. administered three injections of either platelet-rich growth factor, which lacked leukocytes, or platelet-rich plasma, which included 8,300 leukocytes/mL, to 144 patients with various degrees of knee osteoarthritis (Kellgren-Lawrence grades 0-4). Though there were no differences between the 2 in these outcomes, both groups shown a substantial improvement in their subjective scores from the International Knee Documentation Committee (IKDC) and Tegner score.[7]

However, compared to the leukocyte-poor group, pain and edema were much more prevalent in the leukocyte-rich group. Twenty percent of PRP patients reported having severe discomfort, compared to seven percent of patients who had a platelet-rich growth factor injection (P ¼ 0.0005). 15% of patients who had a PRP injection and 4% of patients who received a plateletrich growth factor injection had swelling (P = 0.03).[7]

Cavallo et al. conducted an in vitro investigation to investigate the effects of PRP on osteoarthritic chondrocytes and pure PRP without leukocytes. Three concentrations of plateletpoor plasma and both formulations were tested: 5%, 10%, and 20%. Increased amounts of prochondrogenic growth factors, including TGF-β1 and fibroblast growth factor-β, were seen in all formulations. However, the preparations also included components like VEGF and PDGFAB/BB that could counteract TGF-β1 and fibroblast growth factorβ's anabolic effects.[7]

Hyaluronan secretion peaked with PRP injection including leukocytes, although chondrocyte cell proliferation peaked at 7 days with PRP without leukocytes. These disparate outcomes emphasize the significance of comprehend the nuances of PRP preparation and demonstrate that the The clinical indication will determine the best formulation.[7]

11. RESTRICTIONS -

There are contradictions in the body of research currently available, despite the fact that PRP can produce positive clinical results and safety profiles. PRP requires careful consideration of several factors. These factors, however, were not covered in this article. Results may vary according on the activator types used, the pathology to be treated, the administration routes and timings, and the way PRP is combined with other therapies. Despite the fact that PRP has been the subject of several study publications, this area still needs closer examination due to the erratic outcomes of various investigations and the lack of a clear approach.[9]

12. POSTOPERATIVE MANAGEMENT -

Starting postoperative mobilization sooner, after the initial swelling and bruising has subsided, appears plausible given the laboratory findings of faster and greater healing with the use of PRP.[10]

Presented with a criterion-based advancement schedule comprising first, the degree of discomfort, the quality of the healed tissue, range of motion (ROM), strength, proprioception, end feel, neuromuscular control quality of ROM, and so on patients will heal quickly. [10]

The administration of postoperative analgesia requires caution. Most patients use both antiinflammatory and analgesic medications together. Introducing GF from platelets to aid in healing while also taking anti-inflammatory drugs at the same time sounds counterintuitive. Mode of action predicated on the suppression of platelet activity. Despite documented research on the relationship between non-steroidal anti-inflammatory medicines (NSAIDs) and the recovery of numerous tissues, including muscle, tendon, and bone, not enough information to recommend their concurrent usage with PRP. Thus, we advise against NSAID usage, if at all feasible, at least two days before to PRP application and over the course of the therapy, typically for two weeks following application.[10]

After receiving PRP for Achilles tendon repair, patients' range of motion returned to normal after 7 weeks as opposed to 11 weeks, and they were able to undergo RTP sooner at 14 weeks as opposed to 22 weeks for the control group, all without seeing an increase in the rate of rupture. Similarly, by the sixth week following total knee arthroplasty, patients had increased range of motion.[10]

Professional athletes who want to return to play as soon as possible have clear benefits, which is why many clinicians who use PRP in their practice would speed up standard rehabilitation processes. The majority of published literature on accelerated return to play (RTP) with professional athletes is anecdotal, and prospective studies are still in the design and early stages of development. One of the main issues is the use of different rehabilitation protocols for the treatment and control arms of the study. It would also be unethical to accelerate the rehabilitation regimen for the control group, increasing their risk of reinjury. [10]

Since there is currently little proof of GF's ability to strengthen and aid in the repair of newly created tissue, several sports medicine doctors feel that rehabilitation regimes ought to stay the same. [10]

PRP has mostly been used thus far in the inflammatory and proliferative phases of recovery, which usually occur in the first six weeks following surgery. It seems sense to presume that as the healing process progresses, PRP injections will have an extra positive impact on the healing process. We're currently, a level 1 research design is being used to investigate this concept.[10]

13. ISSUES REGARDING BILLING AND REIMBURSEMENT -

Another concern regarding the use of platelet-rich plasma (PRP) therapy relates to billing and the potential lack of reimbursement for the procedure. The Current Procedural Terminology (CPT) code for PRP injection, implemented on July 1, 2010, is 0232T, which describes “Injection[s], platelet-rich plasma, any tissue, including imaging guidance, harvesting, and preparation when performed.” This code is classified as a temporary category 3 code, which is utilized for emerging technologies, services, and procedures. The purpose of this classification is to facilitate data collection that may be necessary for future Food and Drug Administration (FDA) approval.[11]

It is vital for patients to be informed that PRP injections may not be fully reimbursed by their insurance providers. This situation can leave patients responsible for significant out-of-pocket expenses, which can be a source of financial stress. Transparency in communication about potential costs and reimbursement issues is essential to ensure patients understand their financial responsibilities.[11]

Additionally, the 0232T billing code encompasses various components of the PRP procedure, including imaging guidance, harvesting, and preparation. Consequently, these aspects cannot be billed separately, complicating the billing process for both healthcare providers and patients.

This all-in-one coding can lead to confusion regarding what is covered by insurance and what patients may have to pay.[11]

The existence of this temporary billing code can create challenges in delivering effective patient care. It underscores the necessity for further research to evaluate the effectiveness of PRP therapy more comprehensively. With more robust clinical data supporting its efficacy, there is a greater chance of establishing a permanent billing code. Such a change would enhance patient access to PRP treatments and encourage broader acceptance of PRP as a legitimate therapeutic option within clinical practice. Ultimately, improved coding and reimbursement frameworks could facilitate better patient outcomes and support ongoing advancements in regenerative medicine.[11]

14. ANTI-DOPING REGULATIONS AND PLATELET-RICH PLASMA -

Anti-doping regulations are crucial for maintaining fairness in sports, and the use of plateletrich plasma (PRP) has come under scrutiny. The World Anti-Doping Agency (WADA) oversees these regulations, monitoring substances that might enhance athletic performance. PRP was initially added to the prohibited substances list in 2010 but was removed in 2011. Initially, the ban applied only to intramuscular injections of PRP, while other administration methods, such as intra-articular or peri-tendinous injections, only required a declaration of use. This distinction arose from concerns that the growth factors in PRP could stimulate muscle satellite cells, potentially leading to increased muscle size and strength beyond normal recovery. Although specific growth factors remain banned unless derived from autologous blood, current formulations of PRP have not been shown to enhance performance beyond typical recovery. As research continues, WADA regularly reviews PRP's status to ensure it aligns with fair competition principles.[12]

Concerns about platelet-rich plasma (PRP) stem from the possibility that its growth factors could stimulate muscle satellite cells, potentially leading to increased muscle size and strength beyond what is considered normal recovery. Specific growth factors, such as IGF-1, VEGF, and PDGF, remain banned in sports unless they are derived from autologous blood preparations. This regulation was implemented to prevent athletes from gaining an unfair advantage through enhanced muscle growth.[12]

While some animal studies have indicated that PRP might speed up muscle regeneration, no conclusive evidence shows that it enhances athletic performance beyond typical recovery capabilities. This lack of evidence has led sports governing bodies to conclude that the therapeutic use of PRP does not violate the principles of fair competition. As a result, PRP is now permitted for medical purposes across various routes of administration, provided it is used ethically.[12]

The World Anti-Doping Agency (WADA) continues to assess the use of PRP as new scientific findings emerge. This ongoing evaluation ensures that regulations remain relevant and effective in maintaining the integrity of sport, balancing the therapeutic benefits of PRP with the need for fair competition among athletes.[12]

15. APPROACHES FOR FUTURE DEVELOPMENT -

Given the conflicting findings from ongoing orthopaedic surgery trials, it is not advisable to utilize platelet-rich plasma (PRP) therapy in clinical settings without careful consideration. While some trials have demonstrated PRP's potential for specific applications, there is currently insufficient evidence to support its widespread use. This uncertainty underscores the necessity for well-designed, controlled clinical trials to clarify the benefits and drawbacks of PRP in regenerative orthopaedics.[1]

Future studies should focus on key indicators, ensuring they are appropriately powered with a sufficient number of participants. Additionally, these trials should involve randomized, controlled designs to provide reliable comparisons. It is crucial that the control group is similar to the PRP group in every aspect except for the application of PRP itself.[1]

Moreover, long-term follow-up evaluations and objective outcome measurements should be prioritized to assess the true effectiveness of PRP therapy over time. A comprehensive description of the PRP's composition and preparation methods must be included in the study assessments to allow for reproducibility and validation of results.[1]

Further research is also essential in the realm of basic science to determine the optimal quantity of platelets and bioactive components needed for achieving superior healing compared to standard tissue repair. Identifying the specific elements that contribute most significantly to healing will be crucial, as well as pinpointing the optimal timing for PRP application within the body's natural healing process to maximize its impact.[1]

Advancements in basic science will play a vital role in establishing detailed guidelines regarding PRP composition and its various applications. Such guidelines will ultimately aid in refining PRP therapy, ensuring it is used effectively and appropriately in clinical practice. By addressing these critical areas, the medical community can enhance the understanding and application of PRP, paving the way for its potential integration into standard treatment protocols in orthopaedic medicine.[1]

The use of biomaterials, cells, and other biological components may improve a number of features of regeneration achieved by PRP therapy. Under these circumstances, PPR administration may be utilized in conjunction with conventional tissue engineering techniques or in condensed forms of tissue regeneration. The literature has examples of the combined use of PRP and bone marrow cells for bone regeneration, or epidermal cells for tendinopathy. Additionally, PRP gel and hydroxyapatite carriers might work well together to promote spine fusion.[1]

PRP's adhesive qualities make it potentially helpful for enhance the transport of cells and factors. This element ought to be examined in further studies. Concentrating platelets from whole blood yields PRP.[1]

With the use of membranes, guided subtraction can further isolate and raise the concentration of a certain element or protein extraction filters. But these techniques the process of separating out a specific growth component, manufacturing is still in their early years. More studies analyzing these methods could result in the creation of PRP treatment that is more specifically focused.[1]

The timing of platelet-rich plasma (PRP) therapy in relation to the body's natural healing process is a critical factor that requires careful consideration for optimal treatment outcomes. Healing typically unfolds through several overlapping phases: hemostasis, inflammation, proliferation, and remodeling/maturation. Recent studies suggest that PRP therapy may be most effective during the early stages of this healing continuum, particularly during the proliferation phase, when the body's regenerative processes are most actively engaged.[1]

The healing process begins with hemostasis, where the body works to stop bleeding and initiate tissue repair. This is followed by the inflammatory phase, characterized by increased blood flow and the infiltration of immune cells to the injury site. These immune cells clear debris and help create an environment conducive to healing. The proliferation phase, which follows inflammation, is vital for tissue regeneration, as new cells and extracellular matrix components form. It is during this stage that PRP therapy can offer significant benefits; the growth factors and cytokines in PRP can stimulate cellular activities, promoting faster and more efficient healing.[1]

However, as the healing response progresses toward a chronic or recalcitrant phase, the likelihood of PRP treatment failing increases significantly. This underscores the importance of administering PRP when the healing environment is most receptive. By understanding the specific phases of healing, researchers can identify phase-specific factors or receptors that interact with PRP, enhancing tissue repair and regeneration. This targeted approach can lead to more effective treatment protocols tailored to individual patients based on their specific healing stages, improving overall recovery outcomes.[1]

Clarifying the timing of PRP effects within the healing process is vital for optimizing its application. Aligning PRP treatments with the natural healing trajectory can maximize the therapy's benefits, potentially leading to quicker recoveries and improved patient outcomes in musculoskeletal injuries. Healthcare providers who grasp the dynamics of healing can make informed decisions about when to incorporate PRP into treatment plans, thereby increasing the likelihood of successful results.[1]

In addition to timing, the financial implications of PRP therapy are an increasingly important consideration. Currently, PRP treatments can be relatively expensive and involve significant technological and procedural investments. Understanding these financial aspects is essential for both patients and healthcare providers. Comprehensive cost-benefit analyses are necessary to assess the financial viability of PRP in the context of orthopedic and sports medicine injuries.[1]

These evaluations should take into account not only the direct costs associated with PRP treatments but also their potential long-term benefits, such as improved patient outcomes and reduced long-term healthcare expenses. By examining both immediate costs and long-term savings, healthcare providers can better justify the use of PRP therapy. Such analyses will support informed decision-making regarding the adoption and reimbursement of PRP therapies in clinical practice.[1]

Ultimately, optimizing PRP therapy requires a dual focus on its timing within the healing process and its financial implications. Ensuring that PRP is administered at the most beneficial time, while also understanding its economic impact, enables healthcare providers to enhance recovery for patients with musculoskeletal injuries. This comprehensive approach could lead to greater acceptance and utilization of PRP therapy, improving patient care and outcomes.[1]

By integrating the science of healing with the economics of treatment, PRP can become a more viable option in modern medical practice, benefiting both patients and healthcare systems alike. As research continues to evolve, understanding the intricate relationship between healing phases and PRP therapy will pave the way for more effective treatment protocols and ultimately lead to better healthcare delivery in musculoskeletal injury management.[1]

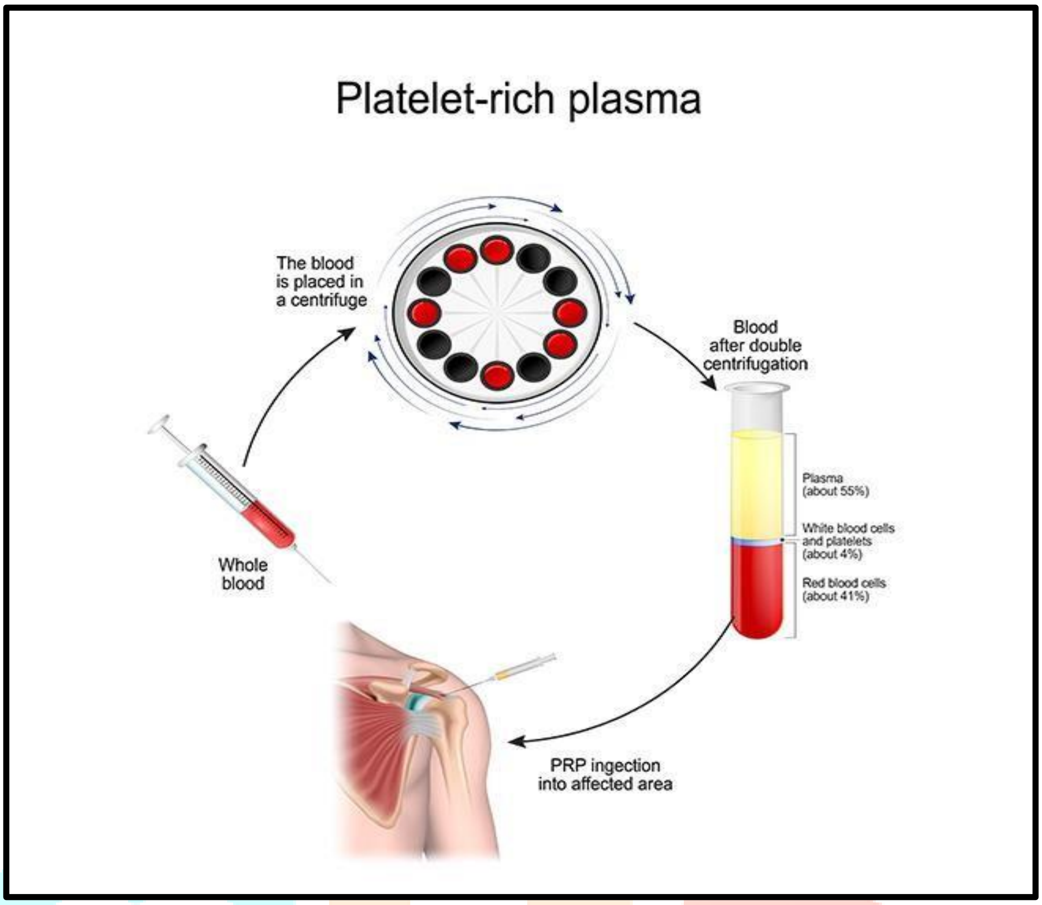

Figure 3: PRP Therapy for Pain [13]

16. CONCLUSION -

PRP treatments are a cutting-edge and intriguing addition to sports medicine and musculoskeletal injury treatment arsenals. However, as many of the concerns regarding PRP mechanisms of action remain unsolved, the responsibilities for the distinct treatment regimens still need to be established. It seems sense to believe that PRP injections following surgery will improve the healing process as it continues. There haven't been any recorded side effects from using it thus far. The advantages of PRP and PRGF injections are becoming more widely recognized as research advances, especially with regard to immediate functional results. PRP can be thought of as an adjuvant to all parts of musculoskeletal surgery, but it should still be seen as experimental due to the existing lack of proof, which does not mean that its usage should be discontinued. We recommend randomized prospective trials using a standardized type of PRP in order to establish its effectiveness and draw definitive results.

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