

Intraarticular Injection of Platelet Rich Plasma in Knee Osteoarthritis

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Abstract

The main purpose of the research is to study role of PRP intra-articular injection in treatment of knee osteoarthritis, and PRP effect on knee osteoarthritis symptoms specially pain, also different methods of preparations

Keywords: PRP , Osteoarthritis , Knee , Intraarticular Injection.

1. Introduction

The word “osteoarthritis” points at a different set of joint abnormalities, commonly referred to complaints of ache and rigidity. It includes devastating and continuous metabolic processes, and many biochemical excitements plus mechanical damage to the joint [1].

Osteoarthritis could be in general classified into primary and secondary. Depending on the Orthopedic Academy of American Surgeons, 1ry osteoarthritis could be referred to damage to the joint that happens without known relatable cause. The articular damage usually include the large ones as the hip joint and knee joint, in addition to some small ones as the hands joints , feet joints , and spine[2].

A number of methods have been identified as non-surgical way for pain control, improve the action, and deformity, and modify the chondral disruption and osteoarthritis with many different improvement ratios[3].

In particular, the new researches of tissue biology give interest to an organization of growth factors for the usual tissues configuration and the response to tissues destruction. PRP is a normal blood concentrates of autologous growth factors. The way is easy, cheap, with little invasion. Autologous PRP is an amount of plasma with a platelet levels greater than normal baseline rates[4].

According to the way of processing the PRP, it can include too white blood cell levels higher than baseline rates[5].

platelets includes a plenty of growth factors and cytokines that are critical for soft tissue improvement and bone mineralization[6].

PRP treatment supplies transmission of a heavily intensified mixture of growth factors to speed up recovery. delivering growth factors found in PRP, has been connected to chondrogenesis in cartilage fixation[7].

2. Anatomy of the knee

The knee joint is the biggest synovial joint within the body. It is formed from the joining of the femur and tibia, that can bear weight, and the joining of the patella and the femur, that permits pulling of the quadriceps femoris muscle to be placed on the anterior surface along the knee on the tibia with no wearing of the tendon Fig (1). A pair of fibro-cartilaginous menisci, in-between condyles of the femur and tibia adjust variations in the form of the articular surfaces while the joints are moved. The details of moves of the knee joint

are complicated, the joint is a modified hinge joint which permits specifically flexion and extension [8].

As each hinge joint, the knee joint is strengthened by two collateral ligaments. additionally , a pair of powerful cruciate ligaments connect the opposite borders of the femur and tibia and keep their positions through flexion and extension [8].

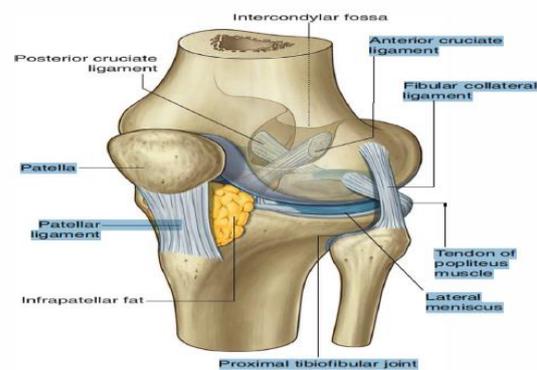


Fig (1) Knee joint ,joint capsule is not shown [8].

2.1 Bone anatomy

The epiphysis of the femur consists of two condyles connected from the front forming the articulation surface of the patella-femoral joint and the intercondylar fossa split them from behind. [9, 10].

The condyles, that are nearly parallel to the cortex of the femoral shaft from the front, project well beyond the shaft emerges at the posterior side. The inner condyle is bigger, more convex, and emerges backwards more than the outer condyle, that is taller in addition to being broader at its connection to the tibia. On each side of the condyles are the medial and lateral epicondyles. The intercondylar notch of the femur contains the anterior and posterior cruciate ligaments [9, 10].

The plateau of the tibia has two articular surfaces, and the inner facet is long in the sagittal plane more than laterally. Both facets are slightly concave in the coronal plane, but the lateral facet is convex in the sagittal plane. So, at the outer part of the knee, the circular femoral condyle stays on the curved surface of the tibia. In-between the tibial plateaus present the medial and lateral intercondylar eminences [9, 10].

The anatomy of the knee considering bones, meniscuses, and ligaments have many biomechanical factors. Initially, due to the form of the femoral and tibial condyles, flexion and extension of the knee joint are not just hinge movements around only one axis of rotation. Through motion, a complex moves of

flexion/extension, internal/external rotations, and anterior/posterior translation happens in the joint. The center of rotation always changes and, when plotted, it J figure around the femoral condyles. So, during complete flexion, the posterior end of the femoral condyles is contacted with the posterior part of the tibial plateau. Moreover, because of the ligamentous hindrance and the asymmetrical contact surfaces of the tibia both femoral condyles, the tibia undergo internal rotation relative to the femur through the initial 10-20° of knee flexion. On the contrary, the tibia is forced on external rotation significantly through the final little degrees of complete extension, as the tibial plateau rolls more forward on the medial femoral condyle than on the lateral condyle [9, 10].

The major surfaces included are both femoral condyles, and the adjacent surfaces of the superior aspect of the tibial condyles. The surface of articulation between the femur and patella are the V-shaped entrench on the distal end of the femur anteriorly where the two condyles meet and the adjacent surfaces on the posterior aspect of the patella. The joint surfaces are all involved within one articular cavitation, as are the intraarticular menisci inbetween the femoral and tibial condyles[8].

3. The Pathophysiology of osteoarthritis

Osteoarthritis is degenerative disease of joints, that influence many persons worldwide. It is a complicated disease whose pathophysiology, affects the tissue homeostasis of articular cartilage and subchondral bone, determine the predominance of destructive processes. A main part in the pathogenesis of articular cartilage is played by cell/extra-cellular matrix (ECM) interactions.

Systemic risk factors for osteoarthritis

1. Age

The age is the main affecting factor of OA. As the age increases, the tensile properties of cartilage in articular cartilage are reduced resulting in accumulation of glycation that leads to mechanical failure [11].

2. Sex

females have a greater rate of pain and disability than males[12]. A hospital-based study detects levels of osteoarthritis as elevated as 68% in females and 58% of males over 65 years[13].

3. Genetic and hormonal factors

usual research of monozygotic (MZ) twins ranging from 48 to 70 years old, with identical genes revealed 65% affection of genetic factors in developing of osteoarthritis. [14] Between 39% and 65% of osteoarthritis in the general population can be referred to genetic factors. Menopausal females are more vulnerable to knee arthritis due to the increased rates of osteocalcin and bone resorption[15].

4. Dietary habits

Rapid alteration in dietary habits and lifestyle by eating of unrefined carbohydrates and fast foods raise the rate of chronic diseases [16]. moreover, chondrocyte is a strong source of reactive oxygen species, that can destroy cartilage collagen and synovial fluid hyaluronate, as micronutrient antioxidants protects tissues from damage, diet contains increased amounts of it can help in preventing osteoarthritis [17].

Local risk factors

1. Joint injury and trauma

Articular cartilage endures great loads from usual activities along the day, in joint injury and trauma the cartilage shows flexibility loss, cell death and decreased loading of the subchondral bone [18].

2. Body weight

Patients with an increased body mass index (BMI) as a measurement of relative weight for obesity, has a direct relation between obesity and knee OA with sever overload and injury to the knee joints [19].

3. Work

Carrying of weighty stuff mainly in farmers, fishermen, builders, and general workers plus climbing up stairs that general laborers usually experience; this kind of heavy work have a powerful association between knee injury and osteoarthritis [20].

4. Physical activities / Sports

Articular cartilage is a strong bearable structure, but clinical experiences show that playing sport may induce force which destroy or injure tissues[21, 22].

General changes in bones and cartilages in OA

OA is a complex disease, its development, progression and acuity may be affected by many factors. The idea of subchondral bone stiffening and elevating bone density in OA is discovered at 1970 by the first investigators Radin and Paul [23].

There is a relation between subchondral bone changes and articular cartilage damage, the bone volume and trabecular thickness raise highly increase with the high stage of cartilage degeneration[24].

In OA the bone becomes more stiff; it can be less capable of absorbing impact loads, that can lead to more stress on the cartilage. [25] The main signs OA are cartilage damage, narrow space, bone hypertrophy and osteophyte forming. Osteophytes are determined as expansion of the bone and cartilage happens at the joints edges. Great relation was noticed between osteophyte volume and local cartilage narrowing. Biomechanical agents help in the osteophyte formation[26].

chondropathy or chondromalacia of the patella is defined usually soft patellar articular cartilage, leads to cartilaginous damage [27]. despite of chondromalacia of the patella is a usual event, its etiology is not clear. In addition to many functional and morphological changes in OA, researches have found many inflammatory

mediators, proteinases, Cell proliferation, biochemical parameters in damage progression[28].

4. Classification of osteoarthritis

Grading of knee osteoarthritis

The Grading for knee osteoarthritis (OA) described by Kellgren, Lawrence (K&L) and Outerbridge Systems. Kellgren and Lawrence grading is greatly used to define and classify osteoarthritis based on radiology. While Outerbridge is the commonly used arthroscopic classification to define and classify osteoarthritis[29].

Kellgren and Lawrence [30] classified osteoarthritis to 5 degrees (0, normal to 4, severe). The changes in radiology that refer to OA are gathered to detect the grades of severity. According to the knee, these signs are:

- (a) development of osteophytes on the joint borders and at the connections of the ligaments.
- (b) narrow gap between joints and sclerotic subchondral bones.
- (c) Cysts and wall sclerosis placed at the subchondral bones.



- (d) distorted ends of the bones.

Normal: no proof of any tear.

Grade 1: narrow joints spaces, eventual osteophytes.

Grade 2: Identified small osteophytes, eventual narrow joints

Grade 3: several, moderate osteophytes, definite narrow joints spaces, little sclerosis, possible deformed bone end.

Grade 4: several big osteophytes, severe joint space narrowing, marked sclerotic areas and definite deformity of bone end.

5. Management of osteoarthritis

Diagnosis

Symptoms

Pain is caused by the inflammation in response to joint irritation, whether caused by the mechanical interference by loose bodies, subchondral fractures, cartilaginous debris engulfed by synovium or other factors [31].

The onset is insidious. A continuous, usually mild, aching pain appears. It may be localized to one side of the joint or may be generalized about the joint. It is aggravated by use and relieved by rest [32].

Stiffness occurs with rest and loosens quickly with activity.

This symptom is prominent upon arising in the morning. It lasts much longer than the simple stiffness that accumulates as a result of lack of activity, but it is less marked than the morning stiffness observed in rheumatoid polyarthritis [32].

Capsular shrinkage and muscle imbalance produce flexion deformity. Limping is common due to pain or deformity. Locking sometimes occurs, possibly because a synovial fringe has been nipped, or occasionally because an osteophyte has broken off to form a loose body [33]

Signs

1) Swelling:

The joint may be swollen from effusion and thickened synovial membrane. In advanced cases the bone ends may be thickened and irregular and osteophytes may be palpable.

2) Stiffness

There is always some degree of limitation of joint movement but never absolute. Movement is painless within the permitted range. Capsular fibrosis is the main cause of stiffness [33].

3) Deformity

The cause of flexion deformity is mainly capsular fibrosis[33].

Varus deformity as patient with knee OA has usually a bow leg, it means that they have a varus alignment of their limbs. at this situation there is a loss of joint space in the medial tibio-femoral region, and the progression of the loss of joint space relate strongly with the severity of the deformity [34].

4) Coarse crepitus

A sense of grating or creaking is often detected during movements due to friction between the roughened surfaces [35].

Investigations:

• Radiography

Radiography is needed in the management of patients when knee ache is repeated at night or not related to activity. If the knee is painful unless functional treatment for OA, radiography can detect unrevealed reasons to diagnose. In a patient of OA, the changes at radiography points minimally to how severe the pain is, and radiography can get clear in patients with OA [35].

• MRI

MRI usually discover abnormalities that explains the existence of OA, although it is not preferred as an

investigation in old patients having chronic knee pain. MRI changes of OA, including meniscal tears, are commonly found in middle age and old adults with and without knee pain [36].

• Arthroscopy

The arthroscopy, recently used in OA usually as a method to transfer surgical medication, may have a main function at the diagnosis of persons with knee ache. Arthroscopy allows magnification of the cartilaginous face and is more precise than plain radiography, CT, or MRI [37].

Non-Operative treatment of osteoarthritis of the Knee

Treating the knee with OA still considered a difficult issue. In spite of advanced pharmacology and inventions in surgery, the perfect way of treatment for patients with progressive OA can be complex. Next, we will explain non-surgical methods used in treating OA of the knee they include the following;

1- Modification of life style

2- Drug Therapy:

- Non-Steroidal Anti-inflammatory drugs
 - Corticosteroids
 - Chondro-protective drugs which include:
 - Glucosamine and chondroitin sulfate
 - Diacerein
 - Hyaluronic Acid
 - Platelet Rich Plasma
- 3- Orthoses.
- 4- Physical therapy[38].

6. Platelet rich plasma

Current options for intra-articular injections include corticosteroids, hyaluronic acid (HA) visco-supplementation, micronized dehydrated human amniotic/chorionic membrane tissues,[39, 40] and (PRP)[41].

Short term symptomatic comfort has been noticed in patient with knee OA that use HA besides corticosteroid injections, however improvement has not been shown to be sustained at 2-year follow-up[42].

At the field of sports medicine, PRP injections used to be effective in the healing of lateral epicondylitis , showing decreased grades of conversion to operative management from medical treatment ,[43]and huge improvement in pain scale ,visual analog scale (VAS) and tendon appearance on (MRI)[44].

Furthermore, PRP has been shown to provide recovery from ache and inflammation associated with OA, so it can be used as effective therapy for the treatment of osteoarthritis.[41, 45] PRP may be obtained from patients on the day of injection and is processed through mild ways, so it is both not expensive and convenient for management of OA[46].

What Is Platelet-Rich Plasma and How Does It Work PRP is a plasma which contains more increased concentration of platelets than whole blood, that exactly

has 150,000 to 300,000 platelets for every microliter.[47, 48]

Although platelets are responsible for hemostasis, these round, a nucleated cells responsibilities are more than just platelet plug formation. Actually, platelets have another function. in between other constituents, platelets contain storage organelles - named granules (dense and α) - which spill their constituents once activated. The dense granules consist of adenosine diphosphate, adenosine triphosphate, serotonin, and calcium; they are responsible for the coagulation process [49].

The α granules contain several growth factors and cytokines which elaborated once platelets are activated by exocytosis to play an important role in the beginning and progression of the three stages of healing which are inflammation, proliferation and remodeling. The main growth factors on which the idea of utilization PRP to allow tissue healing is relied include the following : [50]

- Platelet derived growth factors.
- Vascular endothelial growth factors.
- Transforming growth factors 1.
- Fibroblast growth factors.
- Epidermal growth factors.
- Hepatocyte growth factors.
- Insulin like growth factors 1 .

growth factors have a direct effect clinically in cases which need immediate healing and tissue regenerations it stimulate angiogenesis , regenerate myocytes and enhance the proliferation and migration of mesenchymal stem cells to the position of injury [50].

Preparations of PRP traditionally have a three- to five fold higher platelet count compared with normal plasma, with some reaching as high as 9.3 times the concentration found in whole blood [51].

There is an argument as to what the perfect platelet concentration of PRP must be. According to Marx, a "therapeutic PRP" must contain a platelet concentration 300% to 400% higher than that of total blood. It has been assumed that lesser concentrate doesn't improve tissue healing and that higher concentrates can be useless [52].

Wound healing process includes three stages:

- (1) the inflammatory stage.
- (2) the proliferative stage.
- (3) The maturation and/or remodeling stage.

The first stage, the inflammatory stage, happens in the first week following injury and includes hemostasis and induction of inflammatory mediators. Tissue destruction activates cyclooxygenase-2 and results in vasodilation. Growth factors attract macrophages and fibroblasts. The proliferative and repair stages occur in the following days to two weeks, with forming extracellular matrix with granulation, contraction, and epithelialization. The remodeling stage lasts for up to 1 year following injury, then collagen and scar tissue formation occurs. Type 1 collagen substitutes proteoglycan and fibronectin to make a course matrix with more tensile strength [53].

To prepare PRP, venous blood is first taken from the patients and centrifuged, creating a concentrated suspension. Due to the differing densities of components of whole blood, spinning down the specimen is able to separate the different constituents into different layers: platelet poor plasma, buffy coat, and red blood cells. Platelets, along with white blood cells (WBCs) and proteins, are found in highest concentration in the buffy coat located between the RBCs and the platelet-poor plasma Fig (15). DeLong et al [54] classified PRP preparations into two separate forms: plasma based and buffy coat based. Plasma-based preparation of PRP attempt to include only plasma and platelets while excluding WBCs. This slower and shorter centrifuge method typically yields products with two to three times the baseline levels of platelets with minimal WBC. In contrast, buffy coat based preparation uses both the platelet-poor plasma and the buffy coat layer. This preparation technique involves higher spin rates and longer centrifugation to produce three to eight times the baseline levels of platelet concentrations but also includes WBC/leukocytes as well as RBCs [54].

PRP contains a high concentration of platelets, which contain more than 1,100 proteins such as growth factors.[55] Platelets have a large role in the initiation of healing as they are in charge of forming the scaffolding for clot formation, which leads to chemotaxis of appropriate cytokines. Platelet α -granules contain growth factors and anti-inflammatory cytokines like insulin like growth factor 1 (IGF-1), IGF-2, vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), fibroblast growth factor (FGF), endothelial growth factor, and PDGF. These are released at the healing site [56, 57] and have been shown to help stimulate the growth of autologous chondrocytes and mesenchymal stem cells, as well as constituents of the extracellular matrix as proteoglycans and types I and II collagen.[58-62] In addition, PRP injections have been shown to increase the mitogenic effect of osteoblasts through the stimulation of TGF- β . [45, 63-65]

Following PRP injections, β -FGF, VEGF, PDGF-BB, and IGF-1 all increase at different points over the next 96 hours, suggesting that PRP activates biological pathways to release growth factors rather than simply delivering growth factors in the concentrate [66]. Similarly, human fibroblasts treated with leukocyte-poor PRP (LP-PRP) demonstrate a significant increase in proliferation with cytokines peaking at various time points after injection [67].

PRP has been shown to simultaneously stimulate anabolic growth factors while reducing catabolic proinflammatory cytokine concentrations [41, 68, 69]. PRP uses this dual effect to stimulate fibroblasts, mesenchymal stem cells, and autologous chondrocytes while also decreasing inflammation through the inhibition of interleukin (IL)-1 mediated nuclear factor (NF) light chain-enhancer NF- κ B activation [70, 71].

Different Preparations

With more than a dozen commercially available PRP preparation systems to choose from, properties of the final product can vary greatly.[66-73] An understanding of the many variables that impact PRP treatment is critical when implementing its use in clinical practice. Interestingly, Magalon et al studied multiple PRP preparations from a single donor and found significant variations when comparing the different systems. They concluded that these different variations could account for the discrepancies noted regarding PRP use in the literature [74].

Fitzpatrick et al evaluated the concentrations of platelets, leukocytes, and RBCs in four different commercially available PRP preparation kits including GPS III (Biomet Biologics), Smart-Prep2 (Harvest Terumo), Magellan (Arteriocyte Medical Systems), and ACP (Arthrex Inc.). The study found that in terms of platelets, ACP (autologous conditioned plasma) produced a product with 1 to 1.7 times the whole blood baseline level of platelets, and Magellan, GPS, and SmartPrep produced products with three to six times the baseline platelet concentrations. For RBCs, ACP reduced the count to almost 0, whereas GPS, Magellan, and SmartPrep reduced the count by three to six times the baseline whole blood levels. When considering WBC concentration, ACP reduced the concentration by 5 to 22 times, nearly eliminating WBCs from the final product. The other preparation kits produced leukocyte-rich (LR) preparations and products with three to five times the baseline levels [75].

One important consideration is the platelet concentration. While clinical improvements in the knee have been seen in platelet concentrations that are two to three times the mean,[59, 60, 62, 76] in vitro studies correlate a higher platelet concentration with an increased amount of growth factors [41, 77]. In vivo studies, however, have not been able to replicate this finding in terms of improved healing and patient outcomes [78]. Filardo et al found patients who received dual-spin PRP injections with theoretically higher platelet counts were more-likely to experience pain and swelling compared with those who received single-spin PRP injections but did not find any important clinical difference in terms of benefits between the two groups [79].

Additionally, some techniques have found the second-spin decreased platelet viability depending on the duration of spin and centrifuge speed.[80] Mazzocca et al studied different platelet concentrations using single and double-spin techniques and found that they were unable to determine which platelet -concentrations and PRP preparations would be optimal for each cell type, suggesting that future research needs to focus on determining optimal PRP preparation for each specific disease [78].

Other variables associated with platelets in PRP include the quantity of granule secretion observed with each patient and the possibility of premature activation caused by smaller bore needles [81].

Another controversial difference in preparations of PRP is leukocyte concentration.[82]PRP is considered either

LR or LP. LRPRP has greater than 100% leukocyte concentration compared with whole blood, whereas LP-PRP has less than 100% leukocyte concentration compared with whole blood [83, 84]. Whether PRP is LR or LP depends on how the sample is prepared. As mentioned previously, plasma-based preparations result in LP-PRP as they exclude WBCs. In contrast, buffy coat based preparations result in LR-PRP. In vitro, it has been shown that there is not a considerable difference between the effect of LR-PRP and LPPRP on wound healing, suggesting that the major benefits of PRP stem from growth factors rather than leukocytes [85].

Raeissadat et al studied LR PRP injections in patients with knee OA and found considerable improvement in pain, stiffness, functional capacity, and quality of life 6 months post injection.[86] However, when comparing LR PRP and LP-RPR, Braun et al reported that LR-PRP led to significantly increased cell death and expression of multiple proinflammatory markers such as IL-1 β , IL-6, interferon gamma, and tumor necrosis factor- α (TNF- α) [84].

Moreover, a meta-analysis by Riboh et al found that LP-PRP resulted in improved outcomes compared with HA and placebo, whereas LR-PRP did not prove to have the same effect [83]. These studies demonstrate that the best evidence for the usage of PRP in the treatment of symptomatic knee OA is with the use of LP-PRP rather than LR-PRP. Also controversial regarding LP/LR-PRP is the difference between acute reactions at the time of injection. Animal and prospective studies have shown that patients receiving LR-PRP are more likely to experience painful reactions [79]. while Riboh et al have shown no differences in acute reactions, such as localized swelling, when comparing the two preparations [83].

Besides using autologous PRP, there is also the option to use allogeneic PRP.[87, 88]Bottegoni et al studied 60 patients with knee OA who were not candidates for autologous PRP due to hematological disorders. These patients received a series of three allogeneic PRP injections spaced 2 weeks apart. This study demonstrated a statistically considerable improvement in the International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and VAS scores at 2 and 6 months compared with baseline, although there was also a statistically significant worsening in these scores from 2 to 6 months. However, 90% of patients were pleased at their six-month assessment as these scores remained improved from baseline. This study suggests that allogeneic PRP is a safe and efficacious treatment for knee OA, especially in patients under the age of 80 with less advanced arthritis [89].

For longer term storage, Wen et al conducted an experiment in which LR-PRP was produced through dual-spin centrifuge and stored in a platelet incubator at 22°C for 7 days with agitation. Platelet and WBC

concentrations were measured daily from the room temperature PRP, whereas growth factor release was measured daily after deep-freeze thawing to induce release. Wen et al found that platelet concentrations were 1.6 to 5.7 times the baseline of the donor whole blood, and the samples maintained this concentration for the full 7 days of storage on agitation. Levels of VEGF, hepatocyte growth factor, IGF-1, PDGF-AB, FGF, and endothelial growth factor were also all increased after PRP preparation and maintained or increased this level throughout storage. This study suggests that storage of PRP preparations on agitation may be possible for storage of PRP between injections[90].

Clinical application

Interest in PRP and its clinical applications has been steadily increasing as more researchers are seeing consistent positive results in multiple fields. With such great success in the treatment of lateral epicondylitis [43, 91].

The first goal of clinical research was to determine if PRP injections were superior to other current injection options in the management of OA

In a U.S. Food and Drug Administration (FDA) sanctioned, double-blind randomized controlled trial, Smith et al evaluated the use of ACP PRP in 30 patients with knee OA who failed at least 6 weeks of nonoperative management. These patients received weekly intra-articular injections of either ACP PRP or saline for 3 weeks and were evaluated for 1 year. This study revealed that patients who received ACP PRP had statistically significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score as compared with baseline as well as placebo group starting at 2 weeks and continuing through 12 months. These results demonstrate that ACP PRP is safe and efficacious for the treatment of knee OA[92].

Raeissadat et al [93] studied patients who received either two PRP intra-articular injections at 4-week intervals or three HA injections at 1-week intervals, the standard timeline for HA, using the WOMAC and Medical Outcome Study 36-item ShortForm Health Survey (SF-36) questionnaires to report patient outcomes. At 12-month follow-up, pain scores were improved in both groups, but PRP scores improved significantly more than HA scores. Other aspects of the WOMAC and SF-36 were improved only in the PRP group, suggesting PRP to be more effective than HA in improving patient quality of life in OA [93].

Cole et al [41] studied patients with symptomatic and unilateral knee OA in a double-blind randomized clinical trial comparing LP-PRP injections and HA injections under ultrasound guidance, and measured outcomes including WOMAC, IKDC, VAS, and Lysholm knee scores for 1 year. No difference was seen between the groups in regard to the WOMAC pain score, but there was a significant improvement in IKDC score and VAS score in LP-PRP compared with HA.

They also found that patients with mild OA and lower body mass index had statistically significant improvement compared with other patients. Additionally, analysis of intra-articular biochemical markers approached statistical significance with a decrease in proinflammatory markers, IL-1 β and TNF- α . [41] In another randomized controlled trial, Lana et al reported that PRP alone showed improved outcomes compared with HA alone, and, interestingly, PRP combined with HA resulted in a further decrease in pain and functional limitations compared with either group alone [94]. Similarly, Russo et al showed that PRP/HA blended injections have higher proliferation rates of chondrocytes and concentrations of glycosaminoglycans when compared with HA individually [95].

Studies have compared PRP to other injection options as well. Forogh et al completed a randomized controlled trial to study PRP injections in comparison to corticosteroid injections and reported that PRP provided superior pain and symptom relief for patients with OA as well as significantly improved their functionality and quality of life when compared with those patients who received corticosteroid injections [96].

Rahimzadeh et al [97] compared the effect of PRP to prolotherapy, an alternative medicine treatment in which joints are injected with hyperosmolar solution. This randomized, double-blind clinical trial showed that in patients with knee OA graded stage 1 or 2 on the Kellgren–Lawrence (K-L) scale, although both groups had improved WOMAC scores at 1 month, 2 months, and 6 months postinjection compared with baseline scores, PRP injections were more effective at improving WOMAC score [97]. The current research supports the main advantage of using PRP, that is, its long-lasting and more efficacious function in restoring articular function as compared with HA injections, corticosteroid injection, and other alternatives such as prolotherapy.

Furthermore, the studies previously mentioned support the combined application of PRP with HA as the optimal injection treatment for OA. Once PRP's effectiveness in decreasing pain and increasing functional status in patients with OA has been established, the next step is to determine the appropriate uses, concentration, and injection schedule. There have also been different timelines for injection administration documented throughout studies. These studies have shown improvement in subjective outcomes such as quality of life and pain in patients receiving PRP regardless of injection schedule, but there has not been consistent timeline used across studies [86].

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