INTRODUCTION

Osteoarthritis (OA) of the knee is one of the commonest problems faced by ageing adults and in order to alleviate the pain and morbidity associated with OA, a variety of non-surgical treatment modalities ranging from oral chondroprotectives, intra-articular steroids to viscosupplements have been tried by pain physicians and orthopaedicians worldwide. Platelet-rich plasma (PRP) is evolving into a promising solution for various orthopaedic conditions like tendinopathies, non-union and arthritis of knee. The success of PRP in treating sports injuries in several high-profile sportsmen has contributed to the hype surrounding the PRP therapy, leading to increasing use of PRP for treating OA knees over the last seven years.

PRP is the plasma fraction of autologous blood with platelet concentration above baseline. Platelet counts of 4-5 times of the baseline (1.5-4.5 × 10^5/μL) label the product as PRP. Autogenous platelet gel, platelet enriched plasma (PeRP) and platelet-rich concentrate (PRC) are the synonyms for PRP.

There are various methods of PRP preparation and at least 25-30 ready-to-use kits are commercially available. Initial studies used PRP prepared in the laboratory by different techniques and based on these studies, the commercial kits have evolved. Broadly PRP can be prepared in two ways: “single-spinning” and “double-spinning”. had prepared PRP in a single-spin technique and open procedure which included micro-pipetting and named the product as EndoRet (plasma rich in growth factors). also prepared PRP by the open technique which involved a single-spin, micro-pipetting and additional white blood cell (WBC) filtration, and their product was leucocyte-poor PRP. have prepared PRP by the double-spin technique and cryopreserved the product and used it at three-weekly intervals.

Centrifugal forces and time, as well as the number of spins (double vs single) alter the PRP product in terms of platelet count and leucocyte concentration. Based on the variability in yield, it became necessary to classify PRP in order to compare studies and two classification systems have evolved. One is the Sports Medicine Platelet-Rich Plasma classification system by , which takes into consideration the activation method (activated or not activated) and the leucocyte count (increased or absent) to divide the PRP into four types, with each having two further subtypes A and B based on the platelet concentration. The other international classification system is the PAW classification.
by DeLong et al., which also takes into consideration the absolute platelet count (P1: low to P4: high), the manner of platelet activation and presence or absence of leucocytes.

**What Does Platelet-Rich Plasma Therapy Do?**

Experts are unsure exactly how PRP therapy may alleviate symptoms for certain orthopedic conditions. Doctors who use PRP therapy to treat osteoarthritis theorize that the platelet-rich plasma might:

- Inhibit inflammation and slow down the progression of osteoarthritis.
- Stimulate the formation of new cartilage.
- Increase the production of natural lubricating fluid in the joint, thereby easing painful joint friction.
- Contain proteins that alter a patient’s pain receptors and reduce pain sensation.

It could be that platelet-rich plasma does all of these things, or none. More large-scale, high-quality clinical studies are needed before scientists can know.

**What Is in a Platelet-Rich Plasma Injection?**

All PRP injections are not the same. The exact make-up of platelet-rich plasma depends on several variables, including the concentration of platelets, the concentration of white blood cells, and the use of additives.

**Concentration of platelets**

Normal blood has 150,000 to 450,000 platelets per microliter (μL), and the concentration of platelets in platelet-rich plasma can vary from 2.5 to 9 times that. Concentration levels depend on the individual’s blood, how much blood was drawn, the centrifuge process (e.g., rotation speed and duration), and other clinical preparation methods.

While it may seem logical that plasma with the highest possible platelet concentration will get better results than plasma with a lower platelet concentration, that is not necessarily the case. One lab study suggested that plasma with concentrations 2.5 times that of normal blood was ideal, and higher concentrations might actually limit new cell growth. More research is needed in this area.

**White blood cell count**

The immune system depends on white blood cells to fight infection, but the cells’ role in PRP therapy is unclear. Some experts suspect that white blood cells inhibit tissues’ ability to heal, perhaps promoting inflammation, scar tissue, and damage to nearby tissues. Other experts think that, while white blood cells may not aid tissue healing, they have no negative effects, or may have beneficial effects.

As with the concentration of platelets, the concentration of white blood cells is determined by an individual’s blood as well as clinical preparation methods.

**Additives**

Some doctors mix additives into the platelet-rich plasma. These additives, called thrombin and calcium chloride, artificially activate the platelets, stimulate clotting, and may enhance platelet-rich plasma’s regenerative properties.

PRP has been used in surgeries to promote cell regeneration since 1987, and a growing body of evidence shows it is a viable treatment for tendinosis. Not until recently, though, have experts researched and debated whether or not platelet-rich plasma (PRP) injections are an effective treatment for osteoarthritis.

Nearly all of the research investigating the use of PRP to treat osteoarthritis and other cartilage defects has been done since 2000, and the vast majority of research articles on the topic have been published since 2010.

Not all studies support the use of PRP to treat osteoarthritis; however, experts who have reviewed the existing body of research believe the evidence is largely encouraging and merits further investigation.

**Knee Osteoarthritis Treated with PRP**

Researchers studying PRP and osteoarthritis often work with patients who have knee osteoarthritis, a condition that experts estimate will affect nearly half of all Americans at some point during their lives. Two clinical studies that examine PRP to treat knee arthritis are described below.

One study, published in 2013, involved 78 patients with osteoarthritis in both knees (156 knees). Each knee received one of three treatments: 1 PRP injection, 2 PRP injections, or 1 placebo saline injection. Researchers evaluated the subjects’ knees 6 weeks, 3 months, and 6 months after injection. Researchers found:
Platelet-Rich Plasma (PRP) Therapy for knee........

- Knees treated with 1 or 2 PRP injections saw a reduction in pain and stiffness as well as improvement in knee function at 6 weeks and 3 months.
- At the 6-month mark positive results declined, though pain and function were still better than before PRP treatment.
- The group that received placebo injections saw a small increase in pain and stiffness and a decrease in knee function.

The platelet-rich plasma used in this clinical study had 3 times the platelet concentration of normal blood and had been filtered to remove white blood cells.

A second, smaller study examined patients who had experienced mild knee pain for an average of 14 months. Each arthritic knee underwent an MRI to evaluate joint damage and then received a single PRP injection. Patients’ knees were assessed at the 1 week, 3 month, 6 month and 1 year marks. In addition, each knee underwent a second MRI after one year. Researchers found:

- One year after receiving a PRP injection, most patients had less pain than they did the year before (though pain had not necessarily disappeared).
- MRIs showed that the degenerative process had not progressed in the majority of knees.

While knee cartilage did not seem to regenerate for patients, the fact that the arthritis did not worsen may be significant. Evidence suggests that an average of 4 to 6% of cartilage disappears each year in arthritic joints.

Not all clinical studies provide evidence that PRP alleviates osteoarthritis symptoms. In several clinical studies PRP injections were no better than a placebo treatment. Even in studies that do provide evidence that PRP works, not all patients benefit.

PRP proponents assert that PRP fails to successfully treat symptoms in some cases because of differences in PRP formulation or injection administration - in other words, certain changes in variables, such as PRP preparation methods, the amount of PRP injected, and the frequency of injections, can make the PRP less effective. Others suggest that PRP therapy may be a passing fad that has limited value.

It may be that PRP therapy, like other osteoarthritis treatments, works for some people but not for others, or works best in conjunction with other treatments, such as physical therapy.

Clinical studies

Over 35 clinical trials have been conducted in the past seven years, which reflects the growing interest in exploring PRP as treatment modality in the OA knee. It is surprising to notice that in all previous studies (case series as well as comparative studies), superiority of PRP has been demonstrated in alleviating pain symptoms and improving knee scores.

Sanchez et al. established the safety of autologous PRP for intra-articular use in the first PRP trial in 2008. It was followed by subsequent studies which compared PRP with hyaluronic acid (HA) and demonstrated the safety profile and beneficial effects of PRP in the OA knee. Compared three PRP injections with three hyaluronic acid injections in their randomized control trial (RCT) on 120 patients and concluded the effectiveness and safety of autologous PRP in early osteoarthritis knee (Kellgren and Lawrence Grades 1, 2 or 3 Osteoarthritis). Better Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and Numerical Rating Scale (NRS) were noted in the autologous PRP group in comparison to the HA group. In their RCT on 120 patients compared four PRP injections at one-week interval with low molecular weight hyaluronan (LMW-HA) and observed better improvement of WOMAC scores at 24 weeks in the PRP group. They did not find any correlation with the grade of OA.

Kon et al. treated 91 patients with three PRP injections at three-week intervals (freeze thawed PRP) and noted improvement at six and 12 months from baseline in International Knee Documentation Committee (IKDC) and visual analogue scale (VAS) scores, with a tendency of worsening between six and 12 months. In a subsequent comparative study, Kon et al. observed better symptom control and sustained effects (better IKDC and EQ-VAS scores) in autologous PRP group (three injections at two-week intervals) compared to high molecular weight hyaluronan (HMW-HA) injections (50 patients) and LMW-HA injections (50 patients). They have established good outcomes (IKDC scores) of intra-articular PRP in early degenerative cartilage lesions. They have quoted on better results in younger patients, low body mass index (BMI) patients and those with less degree of cartilage degeneration. They also followed the same
patients for two years and noticed sustained improvement compared to baseline in the PRP group than HA, with a slight worsening after the first year. However in their recent RCT, they found a similar benefit in both HA and PRP groups in early OA.

Sanchez et al.19 in their RCT of 176 patients with Ahlbacks grade 1-3 OA compared three PRP injections at one-week intervals (79 patients) with those of HMW-HA (74 patients). The primary outcome measure was the percentage of patients having a 50% decrease in the WOMAC pain subscore. The secondary outcome measures being other WOMAC subscores, Lequesne index and Osteoarthritis Research Society International (OARSI) responders. They noticed better outcomes in the PRP group at 24 weeks in respect to primary outcome. No differences for secondary outcome measures and amount of acetaminophen consumption were observed.

Similarly better outcomes were documented in the PRP group in comparison to HA groups at six months by Li et al.20 and Say et al.21 in their prospective studies.

Patel et al were the first to compare normal saline (physiological control) with PRP and established the superiority of PRP over placebo as manifested by improved WOMAC scores which were sustained at six months. They noticed that patients were experiencing benefits as early as 18 days and also noted a slight worsening of benefits by six months, based on which they hypothesized that anti-inflammatory role could be the reason for the clinical effect, as for chondral remodelling it would have required much more time and would have given much sustained results.

There is also a lot of confusion regarding the dosage schedule of PRP for OA knees. Initial studies used three injections at three weekly intervals (without any rational though); probably in a bid to compare with HA which is used similarly. The literature is confusing, with studies available which have used two injections, three injections to four injections. The duration between injections is also variable (one week to four weeks). We were the first to compare two different PRP injection groups, and found that single injection was as good as two injections of PRP, shown by similar improvement in WOMAC scores. Recently Görtemli et al.23 in their double-blind placebo-controlled randomized trial noted a statistically significant improvement in the IKDC and EQ-VAS scores in all the treatment groups compared with the control group (Normal Saline). The knee scores of patients treated with three PRP injections were significantly better than those patients of single PRP and HA groups.

Another alternative is to use PRP at yearly intervals or when the patient demands it again after the effect wanes out. Gobbi et al.24 have used PRP at yearly interval and established the clinical efficacy. A lot more research in this direction needs to be carried out as to how long we can prolong the pain-free status with multiple yearly injections.

Hart et al.25 have used another interesting approach in their trial wherein they compared PRP (50 patients) with 1% mesocaine (50 patients) in knee articular damage grade 2 (fissuring and fragmentation). The PRP group received a total of nine injections within a year. The first six injections (loading dose) at weekly interval followed by a three-month gap; followed by three injections at three month interval (maintenance dose). They noticed a better improvement of PRP groups at 12 months with respect to IKDC, Tegner, Lysholm and Cincinnati scores. However, no significant influence on cartilage was observed in magnetic resonance imaging (MRI). So, no clear benefit of such PRP loaded procedure could be validated.

Hassan et al.26 looked at 20 patients with mild to moderate OA, giving 5 mL PRP at monthly intervals for six months (six injections); they noticed significant improvement in knee stiffness, IKDC scores and VAS scores compared to baseline. Maximal improvement was obtained in patients with young age, less BMI and short disease duration.

Majority of the previous studies have included early OA for PRP therapy and consistently showed benefits in terms of symptomatic improvement. Kon et al.27 and Hassan et al.28 have compared early OA with late OA and found better results in early OA. Recently Sánchez et al.29 and his team have described a novel approach of PRP delivery in severe OA by intraosseous infiltration of PRP in subchondral area of femoral condyle, tibial condyle and patella. They also simultaneously gave intra-articular injections of PRP for addressing synovial and cartilage pathology in OA.

Another interesting approach towards PRP administration in OA is the use of photo-activated PRP (PA-PRP). Paterson et al.30 in a randomized controlled pilot study (23 patients) observed the safety profile and feasibility of use of PA-PRP in OA knee. Better
scores were observed in comparison with the HA group. However, studies are required to compare the PA-PRP with PRP to show any additional effect of photo-activation over conventional PRP.

There have been a few studies29,30,31 demonstrating the PRP efficacy over HA in hip OA. Mei-Dan et al.32 demonstrated better outcomes in the PRP group at 28 weeks in talar osteochondral lesions.

With the availability of commercial PRP kits in market, more and more people can receive the treatment. However, it is advisable for the clinicians to not get carried away with the initial results and to keep track of the patient’s outcome so as to contribute to the existing literature. It is also advisable to look at the yield and the product obtained to classify the PRP type.

Anitua et al.33 had postulated that PRP in combination with HA may be synergistic, by enhancing the migratory potential of fibroblast based on her in vitro studies. The same has also been supported by Mar-motti et al. in his in vitro study34. Both HA and PRP are biological approaches and their use may be critical in the initial phase of OA environment where tissue healing may benefit. Based on these concepts Andia et al.35 have expressed that HA+PRP may be better than PRP alone. Dallari et al.31 in their RCT in hip primary OA compared ultrasound guided injections of PRP, HA and HA+PRP and noticed a significant improvement in WOMAC and Harris Hip score in the PRP group over HA. However, the addition of PRP+HA did not lead to significant improvement in pain symptoms. A recent RCT by Lana et al.36 compared HA+PRP versus PRP versus HA in mild to moderate knee OA and noticed better outcomes in the HA+PRP combination over HA alone up to one year and over PRP alone up to three months. They also noted better functional outcomes in the first 30 days after treatment in the combination group over HA and PRP alone groups. Clinical studies on combination therapy are limited and further well-designed studies with a larger sample size are required before a definitive comment can be made. Several key aspects concerning molecular weight, ideal combination and dosage schedule of both need to be evaluated before conducting clinical trials. HA+PRP definitely seems like a good future option.

CONCLUSION

The present state of knowledge holds promise for PRP of certain specifications for pain management in the early OA knee. PRP has consistently been shown by various clinical studies to be superior to HA. Nevertheless, a lot of grey areas remain in our understanding of PRP and OA, and many more focused clinical and in vitro studies are required. HA+PRP seems to be an evolving future trend. Researchers are also focused on developing a better PRP product by combining it with various molecules such as gelatin, chitosan and others. PRP is definitely there to stay for OA therapy use in future.

REFERENCES


