Editorial

Platelet-rich Plasma in Osteoarthritis Knee: Status Report

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 treatment modalities ranging from oral steroids to viscosupplements have been tried by pain physicians and Orthopedicians. Platelet-rich plasma (PRP) has come as a promising solution to various orthopedic 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 PRP therapy. There has been significant usage of PRP for treating OA knees since last 5 years and the data so far has been promising.

The pathogenesis of OA is primarily because of the alteration of normal metabolism within joint, which favors increased catabolism and decreased anabolism. Platelet-rich plasma appears to be a biological process of healing aided by the pool of growth factors within alpha granules of platelets. Platelet-rich plasma is the plasma fraction of autologous blood which has a platelet concentration above baseline. Platelet alpha granules contain and release numerous growth factors, inwcluding hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-b (TGF-b).[1] Platelet-rich plasma helps in addressing the osteoarthritic joint by acting at various levels. First, they help in improving the cartilage structure by decreasing catabolism, improve anabolism, increase type 2 collagen and prostaglandin synthesis, and hence promote overall chondral remodeling. Second, PRP targets synoviocytes and promotes hyaluronic acid (HA) secretion by increasing expression of hyaluronase synthase 2 (HAS-2). It also switches angiogenesis to a more favorable and balanced state. Third, PRP might also influence the apoptotic pathway by down regulating the expression of programmed cell death 5 (PDCD5), thus inhibiting the apoptosis of osteoarthritic chondrocytes. However, the last and probably the most important mechanism of action that explains the well-documented pain reduction, which is also the most prominent and disabling symptom of knee OA, seems to be the anti-inflammatory and anti-nociceptive role (by regulation of nuclear factor-kappaB and cyclooxygenase-2).

Sanchez et al[2] established the safety of autologous PRP for intraarticular use in the first PRP trial in 2008. It was followed by subsequent studies that compared PRP with HA,[3-6] and demonstrated the safety profile and beneficial effects of PRP in OA knee. Spakova et al[3] compared PRP injection with HA in their randomized clinical trial (RCT) on 120 patients and concluded the effectiveness and safety of autologous PRP in early OA knee (Kellgren and Lawrence grades 1, 2, or 3 osteoarthritis). Better WOMAC scores were noted in autologous PRP group in comparison to HA group by Cerza et al[4] in their RCT on 120 patients. Kon et al[5] observed better symptom control and sustained effects in autologous PRP group compared to HA injections in their initial study. Kon et al[6] have established good outcomes (IKDC scores) of intraarticular PRP in early degenerative cartilage lesions. They have stressed on better results in younger patients, low body mass index patients, and those with less degree of cartilage degeneration. They also followed the same patients for 2 years and noticed sustained improvement compared to baseline in PRP group than HA, with a slight worsening after 1st year.[7] However, in their recent RCT they found similar benefit in both HA and PRP group in early OA.[8] We 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 6 months.[9] We also noticed that patients were experiencing benefits as early as 18 days and also noted a slight worsening of benefits by 6 months, based on which we hypothesized that anti-inflammatory role could be the reason for clinical effect, as chondral remodeling would have required much more time and would have given much sustained results.[10] Sundman et al[11] have demonstrated the anti-inflammatory and anti-nociceptive activities of PRP.

There is also a lot of confusion regarding dosage schedule of PRP for OA knees. Initial studies used three injections at three weekly interval (without any rational though), probably in a bid to compare with HA which is used similarly. Literature is confusing with studies available that used 2 to 4 injections. Duration between injections has also varied between 1 to 4 weeks. We were the first to compare between two different PRP injection groups, and found that single injection was as good as two injections of PRP.[9] Whenever PRP has to be used multiple times, it is advisable to freshly prepare PRP each time rather than cryopreserving the same. Kon et al[5,6] in their initial studies used three injections at three weekly intervals. They had prepared the PRP at first time and cryopreserved the PRP for further injections. We had expressed our concern regarding cryopreservation as it is known that the platelets properties would be lost.[12] Roffi et al[13] in their *in vitro* trial have demonstrated the effects of cryopreservation on PRP.

Another alternative is to use PRP at yearly intervals or when the patient demands it again after the effect wanes out. Gobbi et al[14] have used PRP at yearly interval and established the clinical efficacy. A lot more study in this direction need to be carried as to how long we can stretch to prolong the pain free status of joint with multiple yearly injections.

The type of PRP to be used is another topic of debate. The confusion is between leukocyte-rich and leukocyte-poor PRP. We had raised our concern regarding the same in our initial report[12] and hence used leukocyte filter in our study. Initial studies used leukocyte-rich PRP and the trend has shifted toward the use of leukocyte-poor PRP attributing to the pro-inflammatory deleterious effects of leukocytes as evidenced in some *in vivo* studies.[15,16] Filardo et al[17] are the only ones to conduct a clinical trial comparing two different PRP preparations: High-concentrate leukocyte-rich PRP *vs* low concentrate leukocyte-free PRP. One hundred forty-four patients were treated and evaluated up to 12 months. Comparable positive results were obtained in both treatments, with the only difference being that the PRP leukocyte group suffered from more swelling and pain reaction immediately after the injections. To add to the confusion, there are some *in vivo* studies that document some beneficiary effect of leukocyte released products for OA knee. There is still a need of research in this topic as to standardize the concentration of leukocytes needed in ideal PRP preparation.

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 on 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[18] have recently postulated that PRP in combination with HA may be synergistic, by enhancing the migratory potential of fibroblast based on the *in vitro* studies. The same has also been supported by Marmotti et al[19] in their *in vitro* study. 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[20] have expressed that HA+PRP may be better than PRP alone. However, this requires further controlled studies before a definitive comment can be made. Several key aspects concerning molecular weight and ideal concentration of both need to be evaluated before conducting clinical trials.

As of present understanding and our evolving knowledge about PRP, it definitely holds scope for pain management in early OA knee. However, there are still a lot of grey areas in our understanding about PRP and OA and many more focused, clinical, and *in vitro* studies are required.

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