Platelet-rich Plasma and Bone Marrow–derived Mesenchymal Stem Cells in Sports Medicine

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Abstract: Regenerative medicine is a fast-growing field in orthopedic sports medicine. Platelet-rich plasma contains multiple factors that have been shown to augment healing, thereby stimulating its use in multiple areas of acute and chronic injuries. Mesenchymal stem cells have pluripotent potential to form into tissues pertinent to orthopedics, such as cartilage and bone. As such, there is been a surge in the research directed toward steering those stem cells into a particular lineage as part of treatment for a variety of soft-tissue, cartilage, and bone pathologies. Overall, there are promising reports of their potential success, but there is a need for continued investigation into the efficacy of platelet-rich plasma and stem cells in sports medicine.

Key Words: stem cells, platelet-rich plasma, BMAC, bone marrow, biological, regenerative

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PLATELET-RICH PLASMA (PRP)

PRP is an above-baseline concentration of platelets in plasma derived from centrifugation of autologous blood.[1] Circulating platelets contain products in their α-granules that are thought to enhance the healing properties of soft tissues. These include growth factors important for cell proliferation, differentiation, and neovascularization.[2,3] PRP has also been shown to contain cell adhesion molecules and chemotactic properties that help recruit mesenchymal stem cells (MSCs) and fibroblasts to the repair site.[4] The rationale, therefore, behind PRP is to concentrate the healing potential of platelets for use as a treatment modality of various conditions.

PRP is produced by centrifugation of autologous whole blood into red blood cells, white blood cells, and plasma containing platelets. The steps involved significantly vary among the several commercial products available. The variability has an ultimate effect on the final composition of PRP, particularly the platelet concentration.[5] More is not always better, as lower and higher platelet concentrations may have a negative effect on neovascularization.[6] Not only does platelet concentration vary, but so does the white blood cell concentration, which likely has a clinical effect; it has been shown in equine models that leukocyte-poor PRP may be more favorable for tendon healing.[7] The advantage of leukocyte-poor PRP over leukocyte-rich PRP has similarly been shown in the treatment of human knee osteoarthritis.[8]

Further variability comes from the clotting method used for activation and secretion of the contents of α-granules. Some commercial preparations use thrombin, which has been shown to cause secretion of most of the growth factors within 1 hour. To slow the delivery of growth factors, some preparations use calcium chloride which extends that period of time up to 1 week.[3] The clotting ingredients themselves may have direct clinical effects, as Han et al[9] showed thrombin to be detrimental to bone osteoinductivity. Overall, the great variability in the end products of PRP makes it difficult to directly compare PRP products from different commercial preparations; this in turn confounds the results of the clinical studies to date.

Soft-Tissue Healing

Although it is beyond the scope of this article to evaluate the use of PRP in various soft-tissue pathologies, such as lateral epicondylitis and Achilles and patellar tendinopathy, the use of PRP in rotator cuff pathology may be pertinent to the prevention of articular cartilage degeneration associated with rotator cuff tear arthropathy. For chronic rotator cuff tendinopathy, Kesikburun et al[10] found no difference in pain, range of motion, or quality of life after PRP injection compared with placebo. Several randomized, controlled trials published on the augmentation of rotator cuff repair with PRP have conflicting results. Jo and colleagues reported on medium to large rotator cuff tears treated with or without PRP augmentation. Their results favored PRP augmentation, yielding a decreased retear rate (3.0% vs. 20.0%) and increased cross-sectional area of the supraspinatus muscle 1 year postoperatively. However, overall satisfaction and function was not significantly different.[11] Zhao et al[12] performed a meta-analysis of 8 randomized, controlled trials evaluating PRP augmentation of rotator cuff repairs and found no overall significant difference in retear rates or clinical scores when compared with rotator cuff repairs without PRP augmentation.[12]

Cartilage Defects

Numerous studies exist evaluating the use of PRP augmentation as part of treatment of cartilage defects in both animal and human models. Milano and colleagues evaluated the effect of PRP with microfracture in full-thickness chondral defects created in sheep. Six months after treatment, they found improved cartilage repair healing in sheep who received microfracture plus PRP compared with microfracture alone.[13] Multiple studies have also shown improved cartilage-healing characteristics of rabbit cartilage defects treated with collagen scaffolds and PRP compared with scaffolds alone.[14,15] Beyond its use with microfracture, PRP has also been shown to improve osteochondral transplantation. Smyth et al[16] augmented osteochondral transplantation in rabbits with either PRP or saline and found improved graft integration and histologic scoring in rabbits who underwent PRP augmentation compared with saline. Siclari and colleagues investigated the use of PRP and scaffolds in humans. Although without

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comparison, the treatment group, which consisted of 52 patients with articular cartilage lesions of the knee who underwent surgical implantation of scaffolds augmented with PRP, experienced significant improvements in outcome scores starting at 3 months postoperatively that persisted through final follow-up of 12 months.[17]

More research is needed, however, as some investigations dispute the effect of PRP. Kon and colleagues evaluated treatments of osteochondral defects in sheep with hydroxyapatite-collagen scaffolds with or without PRP compared with no treatment. They found improved bone regeneration and cartilage integration in the treatment group with a scaffold alone compared with a scaffold augmented with PRP.[18] In addition, Serra et al[19] evaluated the use of PRP for full-thickness cartilage defects in rabbits and found no significant difference in macroscopic or microscopic evaluation at 19 weeks.

Osteoarthritis

Several systematic reviews and meta-analyses evaluating PRP as treatment for knee osteoarthritis have been published with favorable results.[20–22] Evaluating the effect of repeated cycles of PRP injections, Gobbi and colleagues randomly chose patients with early osteoarthritis to receive either 1 cycle (series of 3 PRP injections 1 mo apart) or 2 cycles, with the second series of 3 PRP injections occurring 1 year after the first cycle. They found that both groups significantly improved at 12 months, but those who received the second cycle showed more improvement than the control at 18 months.[23] In a systematic review of 3 overlapping meta-analyses, Campbell and colleagues found that intra-articular PRP injections produced superior clinical results over either placebo or hyaluronic acid injections starting at 2 months postinjection all the way to 12-month follow-up. All studies found significantly improved Western Ontario and McMaster University Arthritis Index and International Knee Documentation Committee scores.[24] Furthermore, plasma rich in growth factors, not just PRP, has been shown to significantly reduce pain while not sacrificing safety as treatment for knee osteoarthritis.[25]

Selecting for the effect of leukocyte concentration on PRP's effectiveness, Riboh and colleagues investigated 9-level 1 or 2 studies and found leukocyte-poor PRP yielded improved clinical results in the form of Western Ontario and McMaster University Arthritis Index scores when compared with placebo and hyaluronic acid. Interestingly, there were more adverse reactions reported in the PRP group, regardless of the leukocyte concentration[8]; this effect from PRP has also been shown by Khoshbin et al.[20]

Although the majority of uses have shown PRP to be safe with minimal side effects, there has been literature suggesting higher rates of adverse reactions when used for the treatment of knee osteoarthritis. This, and the conflicting clinical results, should encourage us to continue to seek the highest quality evidence to determine the true effectiveness of PRP. Today, it serves as an important tool in the armamentarium of the sports medicine physician as the potential role of PRP continues to grow and be further developed.

BONE MARROW–DERIVED MSCs

The popularity of MSCs originates from their pluripotent potential to differentiate into fat, cartilage, and bone.[26,27] Osteogenic derived stem cells by way of bone marrow aspiration yields a mixture of hematopoietic and nonhematopoietic precursors, red and white blood cells, and platelets.[28] When centrifuged and concentrated, the nonhematopoietic precursors and platelets can be isolated. This isolate contains a variable number of stem cells depending on the source of the harvest. Autologous harvest from bone marrow of the iliac crest has been shown to provide the greatest number of bone-forming MSCs compared with other osseous sources.[29] Once harvested, the aspirate contents are either subjected to a 1-step centrifugation process to yield bone marrow aspirate concentrate (BMAC) or the aspirate can be further expanded to increase the concentration of MSCs.[30] The ability of these stem cells to differentiate into a particular lineage and the paracrine ability of stem cells to release growth factors are of interest in the treatment of orthopedic conditions, particularly because the pluripotent potential of the stem cells include tissues pertinent to orthopedics.[31] Several applicable areas include its use in the treatment of meniscus and rotator cuff tears as well as cartilage defects and osteoarthritis of the knee.[26]

Soft-Tissue Healing

For meniscus and rotator cuff healing, animal studies have yielded promising results that have yet to be investigated extensively in the human population. In a rabbit model, Angele and colleagues treated meniscal defects with either blank scaffolds, scaffolds with bone marrow–derived MSCs, or nothing. The control groups showed fibrous healing patterns, whereas the group that received scaffolds with bone marrow–derived MSCs showed a higher proportion of menisci that healed with meniscus-like fibrocartilage.[32] Zellner and colleagues similarly created a meniscal repair model by using scaffolds with or without PRP, cultured MSCs, noncultured MSCs, and bone marrow to treat circular defects in the avascular zone of rabbit menisci. Although defects treated with scaffolds augmented with cultured MSCs showed fibrocartilage repair tissue, the defects treated with scaffolds augmented with noncultured MSCs showed complete integration of the scaffold with meniscus-like repair tissue.[33] In a human cohort, Vangsness et al[34] used allogeneic stem cells and found increased meniscal volume in knees treated with stem cells after partial medial meniscectomy compared with knees not treated with stem cells. Further investigation is needed in terms of the human clinical application of MSCs for the treatment of meniscus tears.

Stem cells have also been investigated for their potential in stimulating rotator cuff healing. Yokoya et al[35] found more type 1 collagen and increased tensile strength at the repair site of rabbit infraspinatus tendons treated with a scaffold and MSCs compared with blank scaffolds, suggesting improved healing response in tendons augmented with MSCs. Gulotta and colleagues[36–39] have also published several reports on their work with MSCs in an animal rotator cuff model. Early on, their group found no difference in collagen fiber organization or biomechanical strength in repairs augmented with bone marrow–derived MSCs compared with controls.[36,37] In subsequent studies, however, they transduced MSCs with membrane type 1 matrix metalloproteinase and scleraxis, both important factors for tendon development during embryogenesis. In doing so, their group was able to improve not only the formation of fibrocartilage but also the biomechanical properties of the tendons at the repair sites.[38,39]

Translating stem cell use to humans, Hernigou and colleagues found a significant difference in healing rates and prevention of retears with the use of bone marrow–derived MSCs. At 6 months, 100% of the tears treated with MSCs healed versus just 67% without MSCs. Furthermore, at over 10-year follow-up, retears were only noted in 13% of those treated with MSCs compared with 54% of those not treated with MSCs.[40] Although potentially promising, continued clinical investigation of the use of MSCs during rotator cuff repair is needed.

Cartilage Defects

In the animal setting, Wakitani and colleagues evaluated cartilage defects created in rabbit knees that were either left untreated or treated with type 1 collagen gel augmented with bone marrow–derived or periosteal-derived MSCs. Not only finding that the reparative tissue of MSC-treated defects was more similar to normal cartilage, they also found complete repair of subchondral bone in defects treated with MSCs.[41] Hui and colleagues treated osteochondritis dissecans in rabbits with a periosteal graft, mosaicplasty, cultured chondrocytes, or cultured MSCs. At 36 weeks, they noted improved healing characteristics in not only the cultured chondrocyte group but similarly improved characteristics in the cultured MSC group.[42]

In the human population, several reports exist on the clinical application of scaffolds augmented with bone marrow–derived MSCs for cartilage lesions of the knee.[43–48] Gobbi and colleagues followed a group of 25 patients with full-thickness chondral defects of the knee treated with implantation of a type 1/3 collagen matrix augmented with bone marrow–derived MSCs. At final follow-up, there was significant improvement in multiple clinical scores. Complete filling of the defect as shown by magnetic resonance imaging was found in 80% of the patients. This work by Gobbi et al[45] provides evidence supporting the effectiveness of a 1-step procedure for cartilage treatment of full-thickness defects of the knee, thus serving as a form of "biologic arthroplasty."

Further supporting the use of bone marrow–derived MSCs, Gobbi and colleagues directly compared BMAC with matrix-induced autologous chondrocyte implantation (MACI) for patellofemoral lesions in 37 patients. Although there was no significant difference in clinical scores measured at 2 years, both groups significantly improved. Magnetic resonance imaging evaluation showed complete filling of the defects in 81% of the BMAC-treated patients and 76% of the MACI-treated patients. After 2 years, there was an increase in clinical scores of the BMAC group and an insignificant decrease in clinical scores of the MACI group. These results support the use of bone marrow–derived MSCs as a treatment option for patellofemoral defects.[46]

Osteoarthritis

Injected MSCs might have the ability to adhere to cartilage injury sites in animals. In a porcine model, Lee and colleagues created partial thickness cartilage defects and subsequently injected either saline or hyaluronic acid in the control groups and bone marrow–derived MSCs with hyaluronic acid in the experimental group. Not only did they observe accumulation of the carboxyfluorescein-labeled MSCs at the cartilage defect sites but also improved cartilage healing in the experimental group compared with the control.[49] In an equine population, Fortier and colleagues created full-thickness defects in the femoral lateral trochlear ridge and performed marrow stimulation with or without the injection of autologous BMAC. They found increased type 2 collagen and glycosaminoglycans as well as improved integration of repair tissue, collagen fiber orientation, and defect filling in the BMAC group compared with the control group.[50]

Investigating its use in humans, Wakitani and colleagues evaluated 24 knees that underwent tibial osteotomy for medial unicompartmental osteoarthritis. Half of the knees received a collagen gel augmented with bone marrow–derived MSCs under a periosteal patch, whereas the other half received untreated collagen gels under a periosteal patch. During repeat arthroscopy, investigators found improved healing of the cartilage defects treated with bone marrow–derived MSCs. Clinically, however, there were no differences in outcome measures.[51] One clinical factor to consider is the potential effect of age on bone marrow–derived MSCs. Stolzing and colleagues found decreased cell numbers and decreased overall capacity of the MSCs derived from older individuals. This may hinder the effectiveness of bone marrow–derived MSCs.[52] However, several human studies suggest a potential role of injected MSCs in the treatment of knee osteoarthritis particularly as evidenced by significant improvements in multiple clinical scores and decreased subchondral bone edema and increased cartilage healing.[53]

From basic science to clinical investigations, the use of PRP and bone marrow–derived MSCs for treatment of various pathologies pertinent to sports medicine has garnered continued popularity. Particular to articular cartilage injury, the ultimate goal is to regenerate normal hyaline cartilage. MSCs have the potential to differentiate into particular cell lineages, which creates the theoretical potential to use them for targeted therapy in specific pathologic conditions. Until that capability is achieved, we continue to use PRP and MSCs in the capacity available. The current literature shows some promise in their clinical potential, but much is to be learned. As such, there is a continued need for high-quality basic science and clinical investigation into the safety and efficacy of both bone marrow–derived MSCs and PRP in the realm of regenerative medicine.

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