

The Effects of Platelet-Rich Plasma on Cartilage: Basic Science and Clinical Application

Lisa A. Fortier, DVM, PhD,* Catherine H. Hackett, DVM, PhD,* and Brian J. Cole, MD, MBA[†]

Platelet-rich plasma (PRP) is emerging as a biological therapy for the treatment of cartilage injuries and for intra-articular application to address knee pain. Basic science studies indicate that PRP stimulates cell proliferation and the production of cartilage matrix by chondrocytes and bone marrow-derived mesenchymal stromal cells and increases the production of hyaluronic acid by synoviocytes. In preclinical animal model studies, PRP slows the progression of osteoarthritis, but there are mixed results after the use of PRP to facilitate the repair of chondral or osteochondral defects. Clinical studies indicate that PRP-bone marrow-derived stromal cell constructs aid in the repair of chondral defects. A clinical benefit from PRP was also shown for 1 year after intra-articular injection in patients suffering from knee pain. Although most studies support the clinical use of PRP for the treatment of cartilage injury and joint pain, improved classification schemes for PRP and more extensive testing and reporting on the contents of the PRP preparation being applied in the study would aid in the development of treatment protocols.

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The simple rationale supporting the use of platelet-rich plasma (PRP) to treat cartilage injuries lies in the concept that PRP provides a milieu of bioactive growth factors.¹⁻⁴ There are numerous growth factors in PRP that stimulate cartilage matrix synthesis and mitigate the effects of catabolic cytokines such as interleukin (IL)-1 and tumor necrosis factor- α (TNF- α). The effect of these growth factors and catabolic cytokines on the regulation of cartilage homeostasis is the subject of frequent review.⁵⁻¹¹ When tested in combination, growth factors have synergistic effects on cartilage matrix synthesis,^{12,13} and they are known to induce further growth factor protein production by neighboring articular chondrocytes.¹⁴

There are several limitations in extrapolating studies using a single or combination of growth factors to PRP preparations for cartilage or joint applications. First, PRP is much more than just platelet α -granules containing a few growth factors. Platelets also store proteins with antibacterial and fungicidal

effects, coagulation factors, and membrane glycoproteins that influence inflammation by increasing the synthesis of interleukins and chemokines.¹⁵ Dense granules in platelets store and release adenosine diphosphate (ADP), adenosine triphosphate (ATP), calcium ions, histamine, serotonin, and dopamine, which are active in tissue homeostasis.¹⁶ Proteomic studies indicate that over 800 unique proteins are contained within platelets.^{16,17} In addition, as the name implies, PRP contains all components of plasma, including hormones, electrolytes, and several hundred other proteins, such as fibrinogen.¹⁸ There are also white and red blood cells in PRP, each with their own bioactive signature on tissue homeostasis. Second, the quantity of growth factors or cytokines used in in vitro or in vivo studies is on the order of a magnitude (μ g quantities) greater than that contained in PRP (ng or pg quantities). This does not imply that growth factors or cytokines in PRP are too dilute to be effective but rather that in vitro and in vivo studies using recombinant proteins do not typically use biologically relevant articular concentrations.¹⁹⁻²² For example, transforming growth factor (TGF)- β 1 has been reported at a concentration of 580 pg/mL in synovial fluid.²² In vivo and in vitro studies aim to deliver 10-200 ng/mL of TGF- β 1.^{23,24} In PRP preparations, the concentration of TGF- β 1 spans the dosage range with reported values from 10 ng/mL²⁵ to 740 ng/mL.²⁶

*Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY.

[†]Midwest Orthopedics at Rush, Rush University Medical Center, Chicago, IL. Address reprint requests to Brian J. Cole, MD, Rush University Medical Center, 1611 W Harrison, Suite 300, Chicago, IL 60612. E-mail: bcole@rushortho.com

Table 1 Summary of In Vitro Studies of PRP on Articular Tissues Including Chondrocytes, MSCs, and Synoviocytes

Cell Type	Classification of PRP ²⁸	Method of PRP Application to Culture	Study Outcome: Effects Because of PRP	Reference
Mature porcine chondrocytes	L-PRP	10% thrombin-activated releasate	Increased cell proliferation, glycosaminoglycan and collagen synthesis	29
Human osteoarthritic chondrocytes	Platelet and leukocyte concentrations not reported.	100% CaCl ₂ -activated releasate	Similar effect on aggrecan, Sox-9, and S-100, as PRP or fibrin	30
Human osteoarthritic chondrocytes	Platelet but not leukocyte concentrations reported.	5% thrombin-activated releasate	Increased cell proliferation, aggrecan and Sox-9 gene expression, and several proteins associated with chondrocyte differentiation	31
Immortalized chondrocytes	L-PRP	100% CaCl ₂ -activated releasate	Decreased NF- κ B and COX-2 expression	32
Human MSCs	L-PRP	10% PRP	Increased cell proliferation and expression of SOX-2	33
Human osteoarthritic synoviocytes	P-PRP	20% CaCl ₂ -activated releasate	Increased hyaluronic acid synthesis	34

Classification system according to Dohan Ehrenfest et al.²⁷

This enormous range in TGF- β 1 concentration emphasizes the differences in PRP preparations and how the preparations are handled before growth factor analysis (native PRP or releasate after the activation of clotting with thrombin) and why it is so difficult to translate studies on recombinant growth factors to those investigating PRP. It also underscores the need for a uniform classification system to bring some uniformity to the field of PRP for use in musculoskeletal therapies.^{27,28}

In Vitro Laboratory Investigations

The application of PRP for cartilage repair or intra-articular therapy is relatively new, and there is little literature to support or refute its use. In vitro treatment of chondrocytes with releasate from thrombin-clotted leukocyte-PRP (L-PRP²⁷) resulted in significantly increased cell proliferation, synthetic rate, and the accumulation of glycosaminoglycans and collagen type II (COL2) compared with controls²⁹ (Table 1). When osteoarthritic (OA) chondrocytes from patients undergoing total knee arthroplasty were cultured for up to 16 weeks while suspended in either commercial fibrin, platelet-poor plasma (PPP), or PRP with mechanical loading of all constructs, there was immunohistochemical evidence of aggrecan, S-100, and Sox-9 but not COL2 in all scaffold types and no immunohistochemical differences observed between the groups.³⁰ The lack of differences between treatment groups should be interpreted with caution because there was no characterization of the PRP with the reporting of platelet, fibrin, or leukocyte concentration and only 1 donor was used to generate the PRP for the study. In a powerful proteomic study, human OA chondrocytes were removed from patients undergoing total hip arthroplasty, and PRP treatment in-

duced the expression of proteins involved in chondrocytic differentiation.³¹ The OA chondrocytes were grown in monolayer or in 3-dimensional fibrin cultures with medium containing either 10% fetal bovine serum, 5% PPP, or 5% PRP for up to 3 weeks. In both monolayer and 3-dimensional culture conditions, PRP was more effective than PPP or fetal bovine serum at increasing cell proliferation and the expression of genes associated with normal chondrocyte phenotype, including aggrecan and Sox-9 with sustained but not increased levels of COL2. Importantly, no increase in COLX expression was noted with the application of PRP, suggesting that in this culture system OA chondrocytes can begin to restore a normal phenotypic expression pattern without proceeding to or through hypertrophy. Recent basic science investigations reveal that at least 1 effect of PRP on articular chondrocytes is inhibition of the transactivating activity of nuclear factor- κ B (NF- κ B) and decreased expression of cyclooxygenase-2 (COX-2), which are both critical regulators of inflammation.³² These data suggest that not only could PRP be a useful scaffold vehicle for delivery of chondrocytes in cartilage repair procedures but that PRP would also stimulate the local host cartilage to contribute to improved repair.

Human mesenchymal stromal cells treated with unclotted, fresh 10% L-PRP showed significantly greater cell proliferation and SRY (sex determining region Y)-box 2 (SOX-2) expression indicative of chondrogenic differentiation compared with control cultures containing 10% fetal bovine serum.³³ Pilot study data in our laboratory suggest that equine mesenchymal stem cells (MSCs) cultured for 3 weeks in PRP gels show increased matrix synthesis compared with those cultured in cryoprecipitated fibrinogen (Fig. 1, Fortier and Hackett, unpublished data, 2011). Synoviocytes isolated from OA patients undergoing total knee arthroplasty and

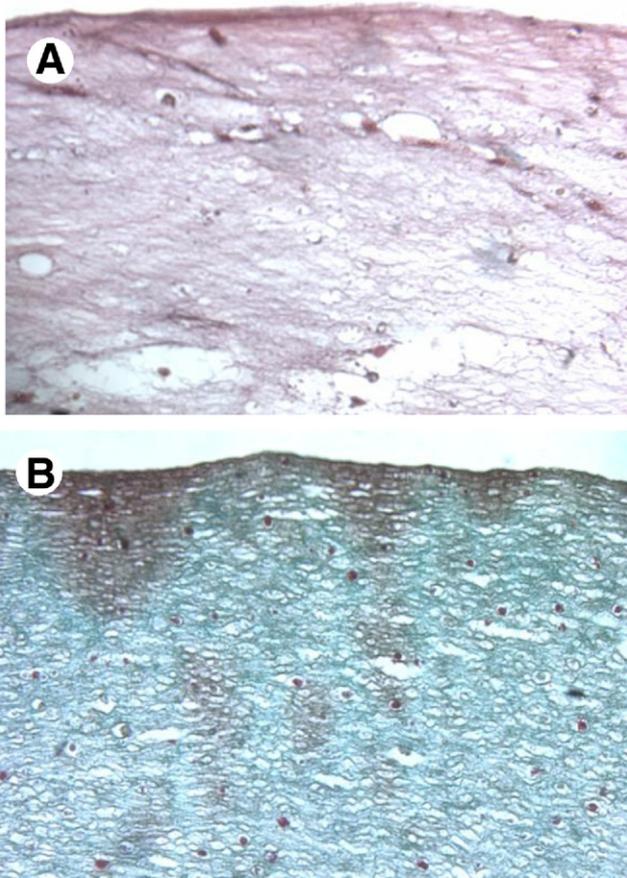


Figure 1 Bone marrow–derived mesenchymal stromal cells cultured for 3 weeks in (A) cryoprecipitated fibrinogen or (B) PRP. Stromal cells cultured in PRP have enhanced proliferation and proteoglycan synthesis compared with those cultured in fibrinogen. Safranin-O fast green stained sections at 40 \times magnification.

cultured in 20% releasate from calcium chloride–activated PRP with no leukocyte contamination²⁷ produced and secreted significantly more hyaluronic acid (HA) compared with synoviocytes cultured in 20% PRP.³⁴ Enhanced HA secretion was also noted in synoviocytes treated with interleu-

kin-1 β , suggesting that pure platelet rich plasma could serve to induce chondroprotection and joint lubrication after intra-articular application even in the face of inflammation. Collectively, these data support the therapeutic potential for PRP in the articular environment with anabolic effects on the cartilage, MSCs, and synovial lining.

Preclinical Animal Model Studies

In preclinical animal studies, PRP has been used in an attempt to repair focal cartilage lesions and for direct intra-articular injection in the treatment of OA (Table 2). In a goat model, PRP was evaluated as an adhesive to secure scaffold-free engineered cartilage constructs into shallow (6-mm diameter \times 0.8-mm deep) osteochondral defects on the femoral trochlea.³⁵ Liquid, unclotted PRP was applied at the base of the construct to increase graft security. At this depth (0.8 mm), the authors' report that calcified cartilage remains, but there were areas of punctate bleeding in the defect. The results indicated that the addition of PRP did not increase graft security or improve integration of the cartilage construct with host tissue in this model as compared with a sutured periosteal flap covering alone. It should be noted that only 2 animals were used in each group with 8 defects per joint, which were treated as independent observations for statistical analyses. The PRP used in this study was generated using the Harvest Technologies System (Harvest Technologies, Plymouth, MA), but no platelet or leukocyte counts were performed to validate the PRP product. This is very important in animal model studies because the type of PRP generated will differ between humans and animals and between animal species. For example, using the Harvest Technologies System, human leukocyte concentration increases in PRP, but in horses the leukocyte concentration remains the same in PRP as in peripheral blood.^{25,36} In a rabbit model, large osteochondral defects (5-mm diameter \times 4 mm deep) were treated with either autogenous PRP in a

Table 2 Summary of Preclinical In Vivo Studies of PRP in the Articular Environment

Animal Model	Classification of PRP ²⁷	Method of PRP Application to Joint	Study Outcome: Effects Because of PRP	Reference
Goat chondral defect	Presumably L-PRP, but values not reported*	100% PRP	No improvement compared to sutured periosteal flap alone	35
Rabbit osteochondral defect	Platelet but no leukocyte concentrations reported	Thrombin-activated on PLGA scaffold	Improved cartilage and bone formation	37
Sheep chondral defect	Platelet but no leukocyte concentrations reported	Ca-gluconate-clotted PRP gel or liquid PRP injection	Improved healing of microfracture site with PRP gel	38
Sheep osteochondral defect	Platelet but no leukocyte concentrations reported	CaCl ₂ -activated on collagen-hydroxyapatite scaffold	Impaired cartilage and bone repair compared to scaffold alone	39
Rabbit ACLT	Platelet but no leukocyte concentrations reported	3% PRP in alginate bead	Decreased progression of OA	40

Classification system according to Dohan Ehrenfest et al.²⁷

*The method used to generate PRP was cited, but no platelet or leukocyte counts were performed to validate the contents of the PRP generated.

Table 3 Summary of Clinical Studies of PRP in the Articular Environment

Trial Type	Classification of PRP²⁸	Method of PRP Application to Joint	Study Outcome: Effects Because of PRP	Reference
Case report	Platelet and leukocyte concentrations not reported	CaCl ₂ -activated injected between fragment and its bed	Returned to play soccer at 18 weeks	41
Pilot study	PRP in combination with PR-FG, platelet but no leukocyte concentrations reported	Bone marrow stem cells on PRP scaffold	Improved Lysholm and RHSSK scores at 6 and 12 months	43
Prospective cohort of PRP vs hyaluronic acid	P-PRP	3 weekly injections	Decreased pain and improved WOMAC scores at 6 months	44
Prospective clinical trial	Platelet but no leukocyte concentrations reported	4 injections every 21 days	Improved IKDC and EQ VAS scores at 6 and 12 months	45

RHSSK, Revised Hospital for Special Surgery Knee Score. Classification system according to Dohan Ehrenfest et al.²⁷

poly-lactic-glycolic acid (PLGA) carrier, PLGA alone, or left untreated.³⁷ After 4 and 12 weeks, the PRP group showed a higher extent of neo-chondrogenesis, increased production of the glycosaminoglycans in the extracellular matrix, and a more normal micro-computed tomography scan of newly formed bone as compared with the untreated or PLGA-alone groups. Another study used a sheep model of full-thickness cartilage defects treated with either microfracture alone, microfracture followed by PRP polymerized in the defect with addition of thrombin, or microfracture followed by intra-articular injection of unclotted PRP.³⁸ After 6 months, the macroscopic scores and cartilage stiffness for the group treated with microfracture and polymerized PRP were significantly better than the other 2 groups. When CaCl₂-activated PRP was combined with a collagen type I/hydroxyapatite scaffold to fill sheep medial femoral condyle osteochondral defects (7-mm diameter × 9 mm deep), histologic scores for bone and cartilage regeneration were adversely affected compared with the repair tissue in defects treated with scaffold alone.³⁹ Similar to the other animal studies platelet, but not leukocyte concentrations were reported. In a rabbit model of anterior cruciate ligament transection (ACLT), PRP or PPP contained in gelatin hydrogels were injected intra-articular twice at 3-week intervals beginning 4 weeks after ACLT. The PRP-gelatin hydrogels significantly suppressed the morphologic and histologic progression of OA compared with PPP-gelatin hydrogels.⁴⁰ The heterogeneity in the preclinical study designs and the lack of consistency in reporting the platelet and leukocyte content of PRP makes it difficult to understand the potential benefits or risks of PRP in cartilage compared with osteochondral repair. It would appear that when just cartilage is involved, PRP is primarily beneficial for repair, but the indications for the addition of PRP to scaffold in osteochondral repair are less clear and in some circumstances could be detrimental to the healing environment.

Clinical Studies

A case report has been published describing the use of PRP to treat a cartilage avulsion (Table 3). In this patient, 2 mL of CaCl₂-activated PRP was injected into the gap between the fragment and its parent bone bed.⁴¹ The treatment was considered successful, with the patient returning to competitive soccer by 18 weeks after PRP. The authors concluded that the addition of PRP augmented reattachment of the cartilage fragment, given the normal guarded prognosis for cartilage injuries that do not extend into the vascularized subchondral region.⁴² A recent pilot study further indicates that cartilage repair can be facilitated by the implantation of bone marrow-derived mesenchymal stromal cells on platelet-rich fibrin glue scaffold.⁴³ In 5 patients, bone marrow-derived mesenchymal stromal cells were mixed with PRP and thrombin in the cartilage defect and secured with a sutured periosteal flap. Patients were followed for 12 months and at both the 6- and 12-month follow-up, clinical scores consisting of Lysholm and the Revised Hospital for Special Surgery Knee Score and magnetic resonance imaging examinations were significantly improved compared with preoperative values.

In an observational cohort of 30 patients with knee pain, intra-articular injections of PRP were compared with HA.⁴⁴ Patients received 3 weekly injections of PRP or HA and were followed for 6 months. This is one of the few studies to date to report the actual PRP preparation and confirm increased platelet counts and a significant decrease of white blood cells. PRP injection improved the success rate of the pain subscale to 33.4% compared with 10% for the HA group ($P = .004$). In addition, PRP significantly improved the percentage reduction in the physical function subscale ($P = .043$) and overall the Western Ontario and McMaster Universities Arthritis Index (WOMAC) ($P = .010$) at 5 weeks compared with HA-treated groups. Kon et al⁴⁵ treated 100 patients (115 knees) with 4 intra-articular PRP injections given every twenty-one days and followed the patients for twelve months.

Patients evaluated in this study included 58 with degenerative chondral lesions (Kellgren 0), 33 with early osteoarthritis (Kellgren I-III), and 24 with advanced osteoarthritis (Kellgren IV). A significant improvement in International Knee Documentation Committee and EuroQuol visual analog scale scores were noted at the end of therapy and at both the 6- and 12-month time points. Eighty percent of patients were satisfied with the treatment, and IKDC objective scores improved from 45.1% to 78.3% at the end of therapy and remained elevated at 73% and 66.9% at 6 and 12 months, respectively. The IKDC subjective and EQ-visual analog scale scores also showed significant improvements at the end of therapy. Older patients had a decreased response compared with younger patients ($P = .049$), and patients over 65 years of age with advanced OA had a significant improvement in only 30% of cases. The authors concluded that treatment with PRP is safe and is effective at improving pain, function, and quality of life in patients with degenerative articular pathology.

The basic science, preclinical, and clinical studies collectively indicate that PRP is promising for the treatment of cartilage injuries and joint pain. Although the mechanism of action of PRP is not elucidated at this time, studies suggest that there is an anabolic effect on chondrocytes, synovio-cytes, and bone marrow-derived stem cells with resultant increases in cell proliferation and matrix production as well as an anti-inflammatory effect via downregulation of known catabolic signaling pathways. With the wide range of methodologies used in each study and the numerous ways to prepare PRP, it is difficult at this time to make firm recommendations regarding the type of PRP to use and for what indications. As the field of PRP in musculoskeletal tissue repair and regeneration moves forward, improved classification method and reporting of the contents of PRP by authors should help delineate which types and volumes of PRP are optimal for specific tissues and acute versus chronic disease states.

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