Platelet-rich Plasma: Current Concepts and Application in Sports Medicine

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Abstract

Platelet-rich plasma is defined as autologous blood with a concentration of platelets above baseline values. Platelet-rich plasma has been used in maxillofacial and plastic surgery since the 1990s; its use in sports medicine is growing given its potential to enhance muscle and tendon healing. In vitro studies suggest that growth factors released by platelets recruit reparative cells and may augment soft-tissue repair. Although minimal clinical evidence is currently available, the use of platelet-rich plasma has increased, given its safety as well as the availability of new devices for outpatient preparation and delivery. Its use in surgery to augment rotator cuff and Achilles tendon repair has also been reported. As the marketing of platelet-rich plasma increases, orthopaedic surgeons must be informed regarding the available preparation devices and their differences. Many controlled clinical trials are under way, but clinical use should be approached cautiously until high-level clinical evidence supporting platelet-rich plasma efficacy is available.

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Platelet-rich plasma (PRP) is defined as a sample of autologous blood with concentrations of platelets above baseline values. Platelets play an instrumental role in the normal healing response via the local secretion of growth factors and recruitment of reparative cells[1] (Table 1). As a means of growth factor delivery, PRP was first popularized in maxillofacial and plastic surgery in the 1990s.[2] Its use in orthopaedics began early in this decade as PRP was used with bone grafts to augment spinal fusion and fracture healing. Although debate continues regarding the potential benefit of PRP to improve bone healing,[3,4] a growing body of laboratory evidence supports the use of PRP injections for the treatment of muscle and tendon injuries and degeneration.[5-15] Despite minimal clinical evidence, recent development of marketed devices to enable PRP preparation in the outpatient and surgical settings has led to an increased use in sports medicine in both Europe and North America.[16]

Preparation

PRP is prepared by taking a sample of autologous, anticoagulated blood and using a centrifuge or filter to separate red blood cells from leukocytes and platelets. With further concentration, plasma is divided into platelet-poor and platelet-rich portions (Figure 1). The efficiency of red blood cell separation and platelet concentration is dependent on the preparation system, but all PRP preparations contain the noncellular

Table 1

Growth Factors in Platelet-rich Plasma

Growth Factor	Source	Function
Platelet-derived growth factor	Platelets	Stimulates cell replication, angiogenesis, mitogen for fibroblasts
Vascular endothelial growth factor	Platelets	Angiogenesis
Transforming growth factor-β1	Platelets	Key regulator in balance between fibrosis and myocyte regeneration
Fibroblast growth factor	Platelets	Stimulates proliferation of myoblasts, angiogenesis
Epidermal growth factor	Platelets	Proliferation of mesenchymal and epithelial cells, potentiation of other growth factors
Hepatocyte growth factor	Plasma	Angiogenesis, mitogen for endothelial cells, antifibrotic
Insulin-like growth factor-1	Plasma	Stimulates myoblasts and fibroblasts, mediates growth and repair of skeletal muscle

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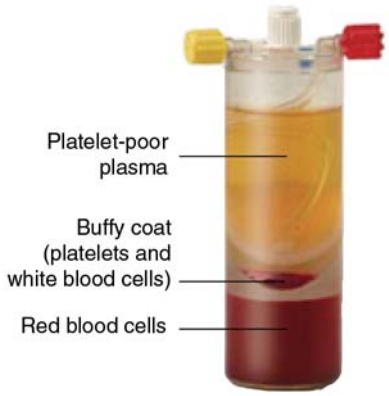
Figure 1



Example of a platelet-rich plasma preparation device (GPS III, Biomet, Warsaw, IN). The buffy coat is platelet-rich plasma. (Adapted with permission from Biomet.)

components of plasma, including clotting factors.

After isolation, PRP can be administered with or without an activating agent. Its combination with calcium chloride and/or thrombin immediately before injection initiates platelet activation, clot formation, and growth factor release at the injection site. Delivery of PRP without an exogenous activator is also commonly performed and has been supported by recent evidence demonstrating that platelets can be slowly activated by exposure to tendon-derived collagen alone.[17,18] For surgical applications, PRP is commonly treated with calcium chloride or thrombin before application, allowing formation of a putty or gel-like clot that can be directly applied or sutured at the surgical site.[19,20]

Several PRP preparation systems are now available that enable efficient preparation for outpatient use (Table 2). Differences such as volume of autologous blood, centrifuge rate/time, delivery method, activating agent, leukocyte concentration, final PRP volume, and final platelet and growth factor concentration differentiate the available systems. Given the qualitative and quantitative differences, reported evidence for clinical effectiveness of PRP cannot be generalized across preparation systems. Hematologic variation between patients (eg, leukocyte count, platelet count) may also affect the final PRP preparation.

Debate continues regarding the optimal quantity of platelets and growth factors required for muscle and tendon healing. Clinically effective PRP was defined as having at least four times the normal platelet concentration;[2] however, efficacy of PRP has been demonstrated with less concentrated preparations.[1,20] The effect of leukocytes present in PRP is controversial. In vitro evidence has demonstrated neutrophil-mediated direct injury to skeletal myotubes, suggesting that matrix metalloproteinases and reactive oxygen species released by neutrophils may exacerbate existing tissue damage.[21]

Given the autologous nature of PRP, safety concerns currently are minimal. As with any injection, strict aseptic technique must be employed to avoid potential infection. Several laboratory studies have also suggested that PRP may have an antimicrobial effect.[22] Relative contraindications include patients with a

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Table 2

Common Platelet-rich Therapy Preparation Systems*

System	Volume of Blood (mL)	Centrifuge Time/Speed	Final PRP Volume (mL)	Final Platelet Concentration (compared with average)	Activator	Level of Growth Factors (compared with average)
Autologous Conditioned Plasma (Arthrex, Naples, FL)†	9	5 min/1,500 rpm	3-5	2-3×	None	PDGF (25×) EGF (5×) VEGF (11×) TGF-β1 (4×) IGF-1 (1×)
Cascade (Musculoskeletal Tissue Foundation, Edison, NJ)‡	9 or 18	First: 6 min/1,100*g*; Second: 15 min/1,450*g*	2 or 4	N/A	Calcium (forms a suturable clot for intraoperative use)	PDGF (N/A) EGF (5-10×) VEGF (5-10×) TGF-β1 (5-10×) IGF-1 (5-10×)
GPS III (Biomet, Warsaw, IN)§	27 or 54	15 min/1,900*g*	3 or 6	4-8×	Calcium chloride/thrombin	PDGF (N/A) EGF (3.9×) VEGF (6.2×) TGF-β1 (3.6×) IGF-1 (1×)
SmartPReP (Harvest Technologies, Plymouth, MA)‖	20 or 60	14 min/1,000*g*	3 or 7	4.4-7.6×	Thrombin	PDGF (4.4×) EGF (4.4×) VEGF (4.4×) TGF-β1 (4.4×) IGF-1 (N/A)

* Information obtained from product manufacturers (platelet and growth factor concentration obtained from unpublished company data for all products listed except for Biomet GPS III [Eppley et al[1]])
† Arthrex: https://www.arthrex.com/innovations/index.cfm?adid=28&CFID=2168033&CFTOKEN=63754575
‡ Musculoskeletal Tissue Foundation: http://platelettherapy.com/
§ Biomet: http://www.biomet.com/biologics/information/pdf/BBI0003.0.pdf
‖ Harvest Technologies: http://www.harvesttech.com/products/smartprepmain.html
EGF = epidermal growth factor, IGF-1 = insulin-like growth factor-1, N/A = not available, PDGF = platelet-derived growth factor, PRP = platelet-rich plasma, TGF-β1 = transforming growth factor-β1, VEGF = vascular endothelial growth factor

history of thrombocytopenia, use of anticoagulant therapy, active infection, tumor, metastatic disease, or pregnancy. There have been no documented cases of carcinogenesis, hyperplasia, or tumor growth associated with the use of PRP.[16]

Given the current economic climate of health care, the cost of any new therapeutic modality is an important consideration. The cost of PRP preparation systems is dependent on the distributing company and on institutional relationships; still, in our experience, the cost for one-time preparation has averaged $150 per syringe. PRP administration is currently considered experimental and is not reimbursed by third-party payers.

Laboratory Evidence

Cell culture studies have provided evidence that PRP can stimulate processes associated with tendon healing. Several investigators have found increased collagen gene expression and increased production of vascular endothelial growth factor and hepatocyte growth factor in human tenocytes treated with PRP,[5,6] although similar increases with platelet-poor plasma were reported in one study.[5] Human tenocytes treated with PRP also have been found to have an increase in *MMP* (matrix metalloproteinase) gene expression, but the significance of matrix metalloproteinases in tendon healing is currently unknown.[5,7] In addition, Kajikawa et al[8] recently reported that PRP stimulates the mobilization of circulation-derived cells to the area of injection and stimulates type I collagen production.

Several investigators have demonstrated greater cell proliferation and angiogenesis in animal tendon models treated with PRP.[9-11] Virchenko and Aspenberg[12] showed greater initial regenerate in a rat Achilles tendon defect treated with PRP and found greater increases in tendon strength compared with controls at 14 days. When mechanical loading was eliminated, there were no differences in strength between the two groups, thus emphasizing the importance of

PRP in ultimate tendon remodeling. The authors[12] concluded that PRP may accelerate the initial inflammatory phase of tendon repair, thereby making cells more receptive to earlier mechanical loading.

In skeletal muscle, growth factors in PRP have been shown in laboratory studies to regulate the inflammatory phase and improve healing. In a mouse model, insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor were found to improve muscle healing and increase fast-twitch strength compared with controls at 1 month.[13] Transforming growth factor-β1 and prostaglandin E_2 were found by Shen et al[14] to be synergistic in regulating the level of fibrosis in skeletal muscle healing, an important factor in restoring full muscle function. Hammond et al[15] recently reported the effects of PRP compared with those of platelet-poor plasma in rats. An improvement in time to recovery was seen only in the high-repetition muscle-injury model, suggesting a greater effect of PRP on myogenesis than on sarcolemmal repair.

Clinical Evidence

Nonsurgical Use

Mishra and Pavelko[17] prospectively evaluated 20 patients who failed nonsurgical treatment of lateral or medial epicondylitis (Table 3). Fifteen patients (14 lateral, 1 medial) received a single PRP injection (GPS [Gravitational Platelet Separation] III System, Biomet, Warsaw, IN), and 5 patients (5 lateral) received a single injection of bupivacaine. The study was nonblinded, and 10 of the 20 patients were randomized to their treatment. At 8 weeks' follow-up, those with PRP injection noted a statistically significant improvement in both visual analog scale (VAS) (60% versus 16%) and Mayo Elbow Performance (52% versus 14%) scores versus those of control subjects. Three of five control subjects withdrew after 8 weeks, thus preventing further comparative analysis. Continued improvement in VAS scores occurred in the PRP group at 6 months, and 93% improvement was observed at final follow-up (mean, 25.6 months).

Preliminary results have been released of an ongoing double-blind, randomized, controlled trial evaluating PRP and cortisone injections for chronic lateral epicondylitis.[23] Of 100 patients, those receiving PRP have demonstrated greater improvements in VAS and Disabilities of the Arm, Shoulder, and Hand questionnaire scores at a minimum 6-month follow-up.

Kon et al[24] recently published a prospective evaluation of 20 male athletes with chronic patellar tendinosis (mean, 20.7 months) who each received three PRP injections into the tendon at 15-day intervals. Patients were allowed to begin light activity after the second injection and were encouraged to begin strengthening activities after the third injection. There were no adverse events, and all participants had improvements in VAS, Medical Outcomes Study 36-Item Short Form, and Tegner activity scores at 6-month follow-up. Eighty percent of participants were satisfied, and 70% showed complete or marked functional recovery. In another uncontrolled series, Barrett and Erredge[25] demonstrated that PRP could be safely injected via ultrasound for plantar fasciitis. Seven of nine patients had complete resolution of pain at 1 year.

Only one clinical report evaluating PRP for muscle injuries is currently available. Sánchez et al[26] prospectively evaluated ultrasound-guided injections of PRP in 22 muscle injuries in 20 high-level professional athletes. They reported full functional recovery in all patients in half the expected recovery time, and no fibrosis was seen.

In a retrospective (level IV) study, Sánchez et al[27] administered intra-articular PRP injections to 30 patients weekly for 3 weeks and compared results with those of 30 patients who had undergone hyaluronic acid substitute injections. The authors noted improved Western Ontario and McMaster Universities Osteoarthritis Index and pain scores with PRP at 5-week follow-up. A randomized, controlled clinical trial is currently under way for further investigation.

Surgical Use

Several studies describe the intraoperative use of PRP. In a case-control study, Sánchez et al[20] evaluated 12 athletes who underwent acute Achilles tendon repair. Six patients were treated with PRP (PRGF [Plasma Rich in Growth Factors] System II, BTI [Biotechnology Institute], Victoria, Spain) at the repair site (Figure 2). The treatment group experienced earlier functional restoration of range of motion (7 versus 11 weeks, $P = 0.025$) and earlier return to jogging (11 versus 18 weeks, $P = 0.042$) and training (14 versus 21 weeks, $P = 0.004$), as well as no wound problems. The PRP group also had less Achilles tendon cross-sectional area after mean of 18 months compared with control subjects ($P = 0.009$), possibly indicating less scar tissue formation. (Cross-sectional area was measured by ultrasonography in this study. The authors used a "trace ellipse method" to calculate it.)

Randelli et al[28] conducted an uncontrolled pilot study of PRP-augmented arthroscopic rotator cuff repair to evaluate safety and outcome. In 14 patients, PRP was injected with thrombin (GPS II Platelet Concentrate System, Biomet) into the footprint after the repair was per-

Table 3

Clinical Evidence for Use of Platelet-rich Plasma in Sports Medicine

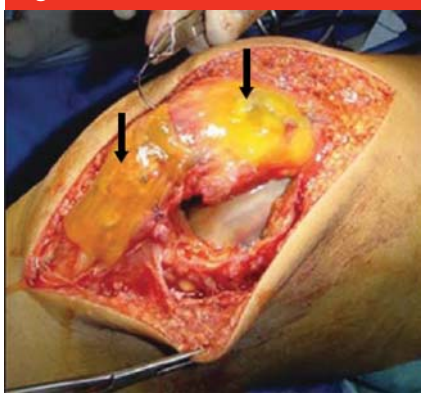
Study	Area of Treatment	Study Type (level of evidence)	No. of Patients	PRP system	Results
Nonsurgical					
Mishra and Pavelko[17]	Lateral and medial epicondylitis	Prospective cohort (II; 10 patients randomized)	20	GPS III (Biomet, Warsaw, IN)	60% versus 16% VAS improvement at 8 wk; 93% improvement at mean 25.6 mo
Gosens et al (unpublished preliminary data, cited in Mishra et al[23])	Lateral epicondylitis	Randomized controlled trial (I)	100	GPS III (Biomet)	Improved VAS and DASH compared with corticosteroid injection at 6 mo
Kon et al[24]	Patellar tendinopathy	Prospective cohort (II)	20	Not reported	70% with complete or marked improvement; 80% satisfied
Barrett and Erredge[25]	Plantar fasciitis	Retrospective cohort (IV)	9	Not reported	Seven of nine patients with complete pain relief at 1 year
Sánchez et al[26]	Muscle injury	Prospective cohort (II)	20	PRGF System (BTI, Victoria, Spain)	Full recovery in all patients in half the expected time
Sánchez et al[27]	Knee osteoarthritis	Retrospective cohort (IV)	30	PRGF System (BTI)	Improved pain and WOMAC scores versus HA injections at 5-wk follow-up
Surgical					
Sánchez et al[20]	Achilles tendon repair	Case-control (III)	12	PRGF System (BTI)	Faster return of ROM, jumping and jogging compared with controls. No wound complications
Randelli et al[28]	Rotator cuff repair	Prospective cohort (II)	14	GPS II (Biomet)	All pts improved VAS, Constant, and UCLA scores at 2 yr. No adverse effects
Everts et al[29]	Open subacromial decompression	Randomized controlled trial (I)	40	GPS III (Biomet)	Faster recovery, earlier return to daily activities, less pain medication requirements
Orrego et al[30]	Anterior cruciate ligament reconstruction	Randomized controlled trial (II)	108	GPS II (Biomet)	Reduced MRI signal intensity in graft at 6 mo. No difference in tunnel widening or bone-tendon interface
Silva and Sampaio[31]	Anterior cruciate ligament reconstruction	Prospective cohort (II)	40	Mini GPS III (Biomet)	No difference in MRI signal intensity at 3 mo
Sánchez et al[32]	Articular cartilage defect	Case report (V)	1	PRGF System (BTI)	Improved pain and return to activity

DASH = Disabilities of the Arm, Shoulder, and Hand questionnaire; HA = hyaluronic acid; PRP = platelet-rich plasma; ROM = range of motion; UCLA = University of California, Los Angeles; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

formed and the irrigation ceased. There were no complications, and, at a mean of 2 years, all patients had statistically significant improvements in VAS, Constant, and University of California Los Angeles shoulder scores compared with preoperative values. The authors are currently conducting a randomized controlled trial to ascertain the efficacy of PRP in arthroscopic rotator cuff repair.

Everts et al[29] recently published results of a randomized controlled trial that evaluated PRP application in patients undergoing open subacromial

Figure 2



Intraoperative use of platelet-rich plasma (arrows) during patellar tendon repair (PRGF System, BTI, Victoria, Spain). (Adapted with permission from Sánchez M, Anitua E, Orive G, Mujika I, Andia I: Platelet-rich therapies in the treatment of orthopaedic sports injuries. *Sports Med* 2009;39:345-354.)

decompression. In the PRP-treated group, patients had a statistically faster recovery with less pain medication requirement, greater range of motion, and greater ability to perform activities of daily living.

Several investigators have evaluated the use of PRP in improving tendon graft healing in tunnels made during anterior cruciate ligament–reconstruction. Orrego et al[30] performed a randomized controlled trial in 108 patients that compared PRP with autologous bone plugs. The use of PRP had an enhancing effect on the graft maturation process, as evaluated by MRI signal intensity, compared with control subjects; however, at 6 months, PRP failed to show a significant effect in the osteoligamentous interface or tunnel widening. Silva and Sampaio[31] also failed to show any difference in signal intensity at the tendon bone interface on MRI at 3 months compared with controls.

Sanchez et al[32] used PRP to augment Kirschner wire fixation of a large (>2 cm) articular cartilage avulsion in a young soccer player and reported excellent results. The patient returned to full competition and on MRI had complete healing of the cartilage lesion at 18 weeks.

Future Directions

PRP represents a possible treatment option for the stimulation and acceleration of soft-tissue healing and regeneration. More substantiated, clinical data are needed to determine its efficacy; standardized preparation and composition will be necessary to compare results. The timing of PRP injection in the therapeutic algorithm must be investigated, and multicenter clinical trials are currently under way to assess the outcomes of using PRP in multiple clinical applications. There have been anecdotal reports of severe pain following outpatient PRP injection. Further investigation into this acute inflammatory response will be necessary for continued PRP use. Post-procedure rehabilitation protocols must also be established to determine optimal muscle and tendon healing.

An important consideration for future use of PRP is concern regarding anti-doping regulations. Currently, the World Anti-Doping Agency code prohibits the use of all growth factor therapies in elite sport.[33] Concerns regarding IGF-1 and its potential ergogenic aid within PRP exist, but they appear to be unfounded. The unbound IGF-1 in PRP has an inadequate half-life to exert systemic effects, and its concentrations are reportedly subtherapeutic by a factor of 500 and thus unlikely to produce systemic anabolic actions.[16]

Summary

Acceleration of muscle and tendon healing with PRP appears to be promising, but there is currently little clinical evidence to support its use. Well-designed, controlled clinical trials are under way and are necessary to determine the therapeutic value of PRP. The use of PRP in anterior cruciate ligament reconstruction, articular cartilage injury, meniscal injury, and knee osteoarthritis is only beginning to be investigated. Further laboratory research must be performed to determine the optimal activation in addition to growth factor, platelet, and leukocyte concentrations. Several PRP preparation systems are now available, and orthopaedic surgeons and sports medicine physicians must be aware of their differences. Given its excellent safety profile and ease of preparation, the use of PRP in sports medicine will likely continue to grow; however, clinical use should proceed cautiously because there is little, if any, high-level clinical evidence supporting the efficacy of this therapeutic modality.

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Citation numbers printed in **bold type** indicate references published within the past 5 years.

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