Scientific Bases of PRP Therapy

87

Corey W. Hunter and Ajax Yang

Introduction

In the simplest of terms, platelet-rich plasma (PRP) is defined as a volume of plasma containing a concentrate of platelets above the baseline of typical/healthy blood levels. While PRP therapy has received significant attention as of late from professional athletes, it has been utilized by physicians for over 30 years in dental and orthopedic surgeries to assist in healing. Its growing popularity with the general public stems from its ability to aid in the repair of soft tissue injuries that are reluctant to heal on their own (i.e., tendon, ligament, and muscle). Moreover, there is no fear of immunogenicity as the whole blood from which PRP is derived is autologous. Given the ever-growing applications and versatility of PRP therapy to facilitate healing in chronically inflamed tissues, it is important to understand and establish the role(s) of platelets as well as the mechanisms involved in normal repair and regeneration.

Microanatomy

Platelets (aka thrombocytes) range from 1 to 4 μm in diameter and are derived from the fragmentation of megakaryocyte lineage in the bone marrow. Platelets contain the following compounds contributing to the different phases of healing (Fig. 87.1).

C. W. Hunter (✉)
Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Ainsworth Institute of Pain Management, New York, NY, USA
e-mail: chunter@ainpain.com

A. Yang
Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Platelet Function and Tissue Healing

Regardless of the tissue type, the normal healing process relies on a combination of two main processes:

1. Regeneration – the replacement of damaged tissues by the surrounding healthy living tissues
2. Repair – scar tissue formation through granulation tissue maturation to substitute the diseased tissues

In order to ensure the PRP technology is applied safely and logically, it is important to understand the fundamentals of platelet function and normal tissue healing stages: hemostasis, inflammation, proliferation, and remodeling.

Immediately following trauma, the locally damaged blood vessels release blood plasma and other cell mediators into the surrounding areas to induce platelet aggregation to form a fibrin clot. This clot plug is the product of the collagen receptor glycoprotein (GPIb/IX/V) binding to the damaged endothelial wall to act as a base for additional aggregation factor, such as platelet integrin αIIbβ3, to adhere themselves to the area. Once the platelets aggregate, they become activated to chemotactically mobilize monocytes, neutrophils, and lymphocytes toward the clot. More importantly, platelet activation and degranulation release seven important growth factors:

- Platelet-derived growth factor (PDGF)
- Insulin growth factor one and two (IGF-1, IGF-2)
- Transforming growth factor-β1 (TGF-β1)
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor (FGF)
- Keratinocyte growth factor (KGF)
- Connective tissue growth factor (CTGF)
- Epithelial growth factor (EGF)

Over 95% of the abovementioned growth factors are released within the first hour of injury and will continue to release growth factors for the next 7–10 days. Fibroblast

T. R. Deer et al. (eds.), *Deer's Treatment of Pain*, https://doi.org/10.1007/978-3-030-12281-2_87

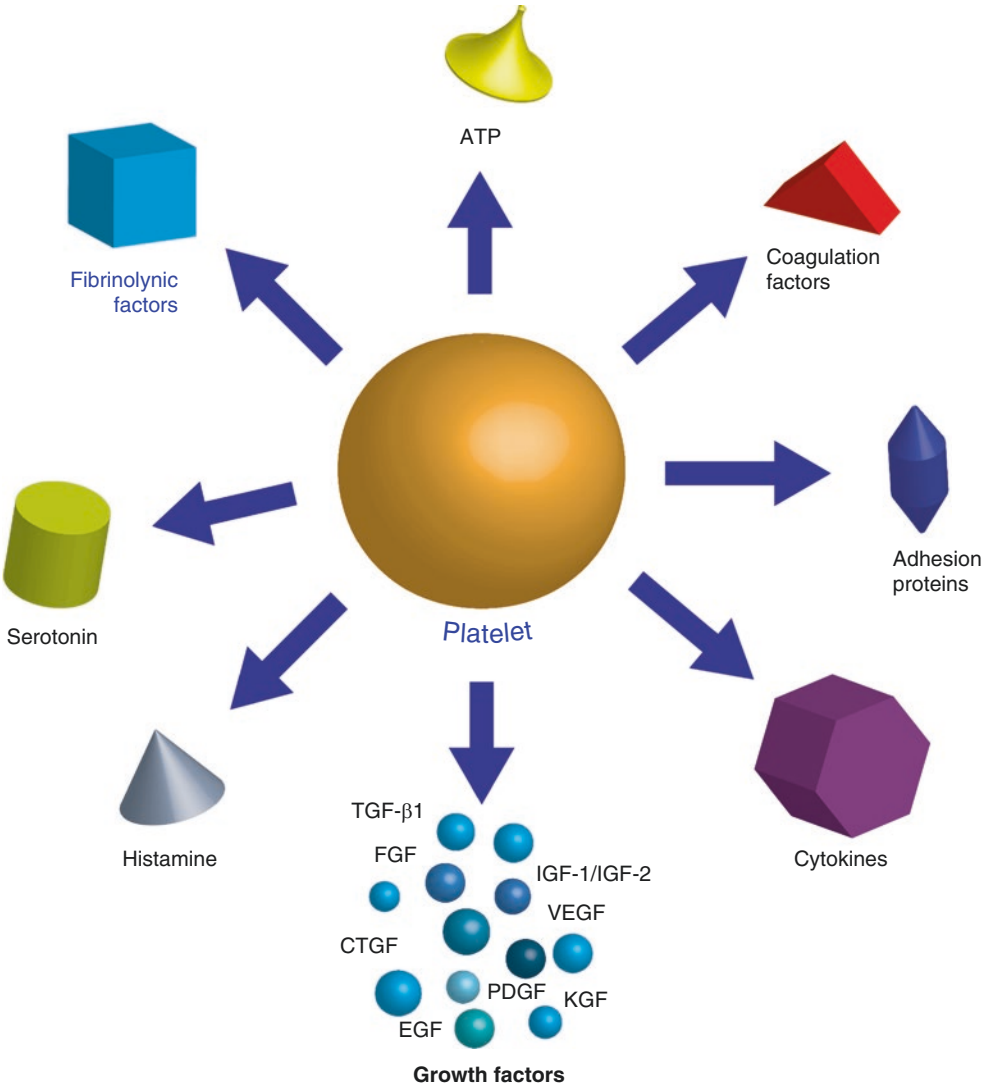

Fig. 87.1 Figure illustrating the different compounds contained within a platelet

stimulation promotes collagen production to replace the fibrin clot during the proliferative phase. Endothelial cells enhance angiogenesis to increase local cellular metabolism. In addition to the growth factors, PRP also contains other bioactive molecules that promote healing. Interleukin 8 (IL-8) promotes angiogenesis. Fibrin, fibronectin, and vitronectin are known cell adhesion molecules for osteoconduction, bone matrix, connective tissue, and epithelial migration during tissue repair.

It is obvious that adequate blood supply is crucial to proper tissue healing. Tendons, ligaments, joints, and certain segments of the muscle all have poor blood supply and are therefore prone to chronic inflammation following initial injury. Chronic inflammation results when acute inflammatory responses are inadequate to restore the prior physiological state. Due to poor blood supply and insufficient endogenous platelet activation/aggregation, macrophages, lymphocytes, fibroblasts, and plasma cells continue to linger at a low concentration without proper healing. Chronic inflammation causes persistent pain, tissue damage, neoneurovascularization, tissue necrosis, and fibrosis. The exact mechanisms causing incomplete acute inflammation are unknown; however, overuse and repetitive microtrauma to a structure have been implicated.

The success and appropriateness of PRP therapy rely on meeting the following conditions:

1. Deliver the high concentration of growth factors to "jump-start" tissue healing in areas with suboptimal blood supply.
2. The target tissue must have the ability to undergo sufficient angiogenesis and accommodate vascularization – thus allowing the body to finish the job.

The rationale is that the high concentration of growth factors merely acts as a beacon to attract and activate endogenous healing molecules that govern protein transcription, cellular division/proliferation, extracellular matrix synthesis,

and collagen formation to the injury site. Continued proliferation of epithelial cells, fibroblastic cells, osteoblastic cells, and mesenchymal stem cells must be sustained by sufficient blood circulation to allow healing to reach completion.

Background and Historical Perspective

By definition, any volume of plasma that contains supraphysiologic platelet count is considered "platelet rich." The characterization of PRP, historically, depended on the platelet concentration alone. However, the concentration and composition of PRP can range widely – this can be due to a number of variables including the physiological state of the patient from which the PRP is derived as well as the method of preparation. This focus on platelet concentration leads to every PRP kit manufacturer claiming their particular product yields the highest platelet counts and/or growth factor concentration. It is important to note that PRP is exempt from the traditional regulatory pathway (human and animal clinical trials) set forth by the Food and Drug Administration (FDA); therefore, any claims by the manufacturers are unverified. Additionally, the ideal platelet concentration is likely to differ depending on tissue type and disease state.

The use of PRP was first introduced in the 1980s in the field of cardiothoracic surgery as a method to conserve intraoperative use of the whole blood. In the 1990s, PRP showed promising results in promoting wound healing in extremity chronic ulcers. Since then, many surgical subspecialties such as maxillofacial, orthopedics, plastics, and podiatry had success of using PRP to achieve excellent outcomes.

The therapeutic effects of PRP rely on complex interactions of platelet-derived proteins, growth factors, cytokines, hormones, and white blood cells (WBC) to create an ideal microenvironment for cellular repair and regeneration at the site of injury. Similar to platelet concentration, WBC quantification has also been studied and used to categorize PRP into:

1. Pure PRP (low WBC, anti-coagulated)
2. Leukocyte-rich PRP (high WBC, anti-coagulated)
3. Pure platelet-rich fibrin (PRF) (low WBC, coagulated)
4. Leukocyte-rich PRF (high WBC, coagulated)

The inclusion of WBC-rich buffy coat has been debated as excessive WBC may cause pain and unwanted scarring. Different cell types cultured in the same PRP yielded different tissue responses. It has also been found that extreme platelet concentrations produced inferior bone regrowth, while moderate concentrations were more effective. Similarly, rotator cuff fibroblasts responded favorably to low and moderate concentrations compared to high concentration. Future research is needed to better define the ideal PRP compositions and concentrations that are disease specific.

Uses and Indications

With the biotechnological advancement in improving the precision and ease of PRP preparation, PRP therapy can be conveniently and safely administered in the office settings. While there are many potential indications and uses for PRP therapy, the most important step begins with patient selection. Physicians should carefully obtain a thorough history including history of injury, location, chronicity, intensity of pain, aggravating and alleviating factors, and prior treatments. Clinical presentation must be supported by imaging to confirm that underlying tissue damage is indeed the symptom/pain generator. After the diagnosis has been established, the standard treatment(s) should be tried first. Similar to rationales that govern regenerative medicine as a whole, PRP therapy candidates typically fall into one of the three groups:

1. Asymptomatic patients with high degeneration risks.
2. Symptomatic patients in the beginning phase of degeneration process.
3. Symptomatic patients in the late phase of degeneration process.

The therapeutic effects of PRP therapy are reduced in older individuals with obesity and advanced stages of degeneration. In contrast, younger patients with lower body indices and early stages of disease demonstrated a more favorable outcome with PRP treatment. Therefore, it is important to present the advantages and disadvantages to all patients considering pursuing PRP therapy:

Advantages:
1. Blood sample is easily and safely obtained from peripheral venipuncture.
2. PRP therapy can be performed in an office setting.
3. It is relatively inexpensive compared to other tissue regenerative options.
4. Since the blood sample is obtained directly from the patient, there is low risk of allergic reaction and infection.

Disadvantages:
1. Injection could be very painful as PRP creates an acute inflammatory reaction.
2. The patient is required to avoid NSAIDS days before and several weeks after PRP administration.

Tendinous and ligamentous injuries are the earliest and common conditions that PRP was used to treat and showed

good outcomes. PRP is particularly effective in treating injured body parts with tenuous blood supply. As hemostasis of the inflammatory cascade is vascular dependent, poor blood supply impedes optimal delivery of endogenous platelets and growth factors to initiate the tissue healing process. Injections of PRP to these areas can essentially mitigate a decrease in vascular perfusion and "jump start" the healing cascade. The common musculoskeletal pathologies encountered by pain management physicians can be grouped into the following:

1. **Tendon/Ligamentous Injury**
   - *Medial/lateral epicondylopathy/epicondylitis*
   - *Medial/lateral collateral ligament injury*
   - *Anterior cruciate ligament injury*
   - *Patellar tendinopathy*
   - *Rotator cuff tendinopathy*
   - *Achilles tendinopathy*
2. **Cartilage Degeneration**
   - *Acetabular labral tear*
   - *Glenoid labral tear*
   - *Osteoarthritis (OA)*
3. **Muscle Injury**
4. **Degenerative Disc Disease**

Contraindications, relative and absolute, for the use of PRP are listed in Table 87.1.

Evidence for Efficacy

The evidence of PRP therapy is rapidly expanding. At the time of this chapter preparation, PRP search on Pumed.gov alone yielded nearly 4000 publications. The evidence supporting the use of PRP in treating musculoskeletal pathology will undoubtedly continue to grow. The highest level of available evidence with the corresponding musculoskeletal pathologies is tabulated in the order of empirical evidence strength (Table 87.2).

Table 87.1 Relative and absolute contraindications for PRP

Relative contraindications	Absolute contraindications
1. Oncological history 2. History of arthroplasty 3. Pregnancy 4. Smoking 5. Systemic disorder	1. Inflammatory arthritis, e.g., rheumatoid arthritis, gout, and ankylosing spondylitis 2. Active local and systemic infection, e.g., septic arthritis 3. Active malignancy 4. Immunodeficiency 5. Bleeding disorder or thrombocytopenia 6. Hypofibrinogenemia 7. Anemia (hemoglobin less than 11 g/dL) 8. Ongoing NSAID or steroid therapy 9. Complicated anatomy 10. Acute injury 11. Inability to obtain consent or follow post PRP therapy care plans

Table 87.2 PRP evidence table

Quality of evidence assessment	Musculoskeletal pathology
I: Evidence obtained from at least one properly randomized controlled trial	Lateral epicondylopathy/ epicondylitis
	Hip OA and labral tear
	Knee pain OA and soft tissue injury
	Maxillofacial surgery
	Shoulder pathology including acromioclavicular joint and rotator cuff injuries
II-1: Evidence from well-designed controlled trials without randomization	Patellar tendinopathy
	Anterior cruciate and medial collateral Ligament repairs
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one research group	Achilles tendinopathy
	Plantar fasciitis
	Medial epicondylopathy/ epicondylitis
	Lumbar facet joint arthropathy
II-3: Evidence obtained from comparisons between times or places with or without the intervention	Degenerative disc disease

Pearls and Pitfalls

- PRP is safe and effective to induce or accelerate healing and pain relief.
- Despite a lack of coverage by the current insurance system, there is good and growing evidence to support the use of PRP.
- Pain physicians should be familiar with the absolute and relative contraindications to ensure patient safety.
- NSAIDs should be held for at least 7 days and 10 days for steroid before initiating PRP therapy. Following PRP treatment, NSAIDS should not begin within 30 days.
- Multiple repeated PRP injections in the same location may be necessary in order to achieve an optimal clinical outcome.
- Future standardized studies are needed to delineate different tissue disease-specific PRP concentration and composition.

Recommended Reading

1. Al-Ajlouni J, Awidi A, Samara O, et al. Safety and efficacy of autologous intra-articular platelet lysates in early and intermediate knee osteoarthrosis in humans: a prospective open-label study. Clin J Sport Med. 2015;25(6):524–8.
2. Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets. 2013;24(3):173–82.
3. Andia I, Maffulli N. Muscle and tendon injuries: the role of biological interventions to promote and assist healing and recovery. Arthroscopy. 2015;31(5):999–1015.
4. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91(1):4–15.

5. Anitua E, Sánchez M, Zalduendo MM, et al. Fibroblastic response to treatment with different preparations rich in growth factors. Cell Prolif. 2009;42(2):162–70.
6. Assoian RK, Komoriya A, Meyers CA, Miller DM, Sporn MB. Transforming growth factor-beta in human platelets. Identification of a major storage site, purification, and characterization. J Biol Chem. 1983;258(11):7155–60.
7. Basso M, Cavagnaro L, Zanirato A, et al. What is the clinical evidence on regenerative medicine in intervertebral disc degeneration? Musculoskelet Surg [Internet] 2017; Available from: https://doi.org/10.1007/s12306-017-0462-3.
8. Bertrand H, Reeves KD, Bennett CJ, Bicknell S, Cheng A-L. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. Arch Phys Med Rehabil. 2016;97(1):17–25.
9. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy. 2012;28(3):429–39.
10. Cavallo C, Filardo G, Mariani E, et al. Comparison of Platelet-Rich Plasma formulations for cartilage healing. J Bone Joint Surg Am. 2014;96(5):423–9.
11. Cerza F, Carnì S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med. 2012;40(12):2822–7.
12. Chen W-H, Lo W-C, Lee J-J, et al. Tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-β1 in platelet-rich plasma. J Cell Physiol. 2006;209(3):744–54.
13. Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA. Platelet-rich plasma: where are we now and where are we going? Sports Health. 2010;2(3):203–10.
14. Crane D, Everts P. Platelet rich plasma (PRP) matrix grafts. Pract Pain Manag. 2008;8(1):11–26.
15. Diehl JW. Platelet-Rich plasma therapy in chronic Achilles Tendinopathy. Tech Foot Ankle Surg. 2011;10(1):2.
16. Ferrari M, Zia S, Valbonesi M, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery. Int J Artif Organs. 1987;10(1):47–50.
17. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop. 2010;34(6):909–15.
18. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med. 2009;37(11):2259–72.
19. Gallin JI, Goldstein IM, Snyderman R. Inflammation: basic principles and clinical correlates. Philadelphia: Lippincott Williams & Wilkins; 1999.
20. Ganio C, Tenewitz FE, Wilson RC, Moyles BG. The treatment of chronic nonhealing wounds using autologous platelet-derived growth factors. J Foot Ankle Surg. 1993;32(3):263–8.
21. Golebiewska EM, Poole AW. Platelet secretion: From haemostasis to wound healing and beyond. Blood Rev. 2015;29(3):153–62.
22. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Am J Sports Med. 2011;39(6):1200–8.
23. Gui K, Ren W, Yu Y, Li X, Dong J, Yin W. Inhibitory effects of platelet-rich plasma on intervertebral disc degeneration: a preclinical study in a rabbit model. Med Sci Monit. 2015;21:1368–75.
24. Gullung GB, Woodall JW, Tucci MA, James J, Black DA, McGuire RA. Platelet-rich plasma effects on degenerative disc disease: analysis of histology and imaging in an animal model. Evid Based Spine Care J. 2011;2(4):13–8.
25. Hamilton B, Tol JL, Knez W, Chalabi H. Exercise and the platelet activator calcium chloride both influence the growth factor content of platelet-rich plasma (PRP): overlooked biochemical factors that could influence PRP treatment. Br J Sports Med. 2015;49(14):957–60.
26. Heldin CH, Westermark B, Wasteson A. Platelet-derived growth factor. Isolation by a large-scale procedure and analysis of subunit composition. Biochem J. 1981;193(3):907–13.
27. Hohaus C, Ganey TM, Minkus Y, Meisel HJ. Cell transplantation in lumbar spine disc degeneration disease. Eur Spine J. 2008;17(Suppl 4):492–503.
28. Jang S-J, Kim J-D, Cha S-S. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol. 2013;23(5):573–80.
29. Karey KP, Sirbasku DA. Human platelet-derived mitogens. II. Subcellular localization of insulinlike growth factor I to the alpha-granule and release in response to thrombin. Blood. 1989;74(3):1093–100.
30. Kepler CK, Anderson DG, Tannoury C, Ponnappan RK. Intervertebral disk degeneration and emerging biologic treatments. J Am Acad Orthop Surg. 2011;19(9):543–53.
31. Kevy S, Jacobson M. Preparation of growth factors enriched autologous platelet gel (2001) Proceedings of the 27 th Annual Meeting of Service Biomaterials. April [Links].
32. Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F. Stimulation of repair in chronic, nonhealing, cutaneous ulcers using platelet-derived wound healing formula. Surg Gynecol Obstet. 1990;170(1):56–60.
33. Kon E, Mandelbaum B, Buda R, et al. Platelet-Rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011;27(11):1490–501.
34. Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. Clin Dermatol. 2007;25(1):9–18.
35. Lind M. Growth factor stimulation of bone healing. Effects on osteoblasts, osteotomies, and implants fixation. Acta Orthop Scand Suppl. 1998;283:2–37.
36. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62(4):489–96.
37. Middleton KK, Barro V, Muller B, Terada S, Fu FH. Evaluation of the effects of platelet-rich plasma (PRP) therapy involved in the healing of sports-related soft tissue injuries. Iowa Orthop J. 2012;32:150–63.
38. Möhle R, Green D, Moore MAS, Nachman RL, Rafii S. Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. Proc Natl Acad Sci. 1997;94(2):663–8.
39. Nagae M, Ikeda T, Mikami Y, et al. Intervertebral disc regeneration using platelet-rich plasma and biodegradable gelatin hydrogel microspheres. Tissue Eng. 2007;13(1):147–58.
40. Nguyen RT, Borg-Stein J, McInnis K. Applications of platelet-rich plasma in musculoskeletal and sports medicine: an evidence-based approach. PM R. 2011;3(3):226–50.
41. Niemansburg SL, van Delden JJM, Oner FC, Dhert WJA, Bredenoord AL. Ethical implications of regenerative medicine in orthopedics: an empirical study with surgeons and scientists in the field. Spine J. 2014;14(6):1029–35.
42. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013;41(2):356–64.
43. Peebooms J, et al. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. Am J Sports Med. 2009;38(2):255–62.
44. Pourcho AM, Smith J, Wisniewski SJ, Sellon JL. Intraarticular platelet-rich plasma injection in the treatment of knee osteoarthritis: review and recommendations. Am J Phys Med Rehabil. 2014;93(11 Suppl 3):S108–21.

45. Ruggeri ZM. Platelets in atherothrombosis. Nat Med. 2002;8(11): 1227–34.
46. Sadoghi P, Lohberger B, Aigner B, et al. Effect of platelet-rich plasma on the biologic activity of the human rotator-cuff fibroblasts: a controlled in vitro study. J Orthop Res. 2013;31(8):1249–53.
47. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. 2012;28(8):1070–8.
48. Sawamura K, Ikeda T, Nagae M, et al. Characterization of in vivo effects of platelet-rich plasma and biodegradable gelatin hydrogel microspheres on degenerated intervertebral discs. Tissue Eng Part A. 2009;15(12):3719–27.
49. Serhan CN, Ward PA, Gilroy DW. Fundamentals of inflammation: Cambridge University Press; 2010.
50. Sun Y, Feng Y, Zhang CQ, Chen SB, Cheng XG. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. Int Orthop. 2010;34(4):589–97.
51. Tetschke E, Rudolf M, Lohmann CH, Stärke C. Autologous proliferative therapies in recalcitrant lateral epicondylitis. Am J Phys Med Rehabil. 2015;94(9):696–706.
52. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. Am J Sports Med. 2011;39(10):2130–4.
53. Tinsley BA, Ferreira JV, Dukas AG, Mazzocca AD. Platelet-Rich plasma nonoperative injection therapy—a review of indications and evidence. Oper Tech Sports Med. 2012;20(2):192–200.
54. Tozum TF, Demiralp B. Platelet-rich plasma: a promising innovation in dentistry. J Can Dent Assoc. 2003;69(10):664–5.
55. Vora A, Borg-Stein J, Nguyen RT. Regenerative injection therapy for osteoarthritis: fundamental concepts and evidence-based review. PM R. 2012;4(5 Suppl):S104–9.
56. Walter JB, Israel MS. General Pathology. 6th ed. Edinburg: Churchill Livingstone; 1987. p. 151–3.
57. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone. 2004;34(4):665–71.
58. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1997;55(11):1294–9.
59. Wroblewski AP, Mejia HA, Wright VJ. Application of Platelet-Rich plasma to enhance tissue repair. Oper Tech Orthop 2010/6;20(2):98–105.
60. Wu J, Du Z, Lv Y, et al. A new technique for the treatment of Lumbar Facet joint syndrome using intra-articular injection with autologous Platelet Rich plasma. Pain Physician. 2016;19(8):617–25.