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PLATELET-RICH PLASMA – THERAPEUTIC CONSIDERATIONS IN REHABILITATION OF MUSCULOSKELETAL CONDITIONS

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ABSTRACT
Since the first use of platelets for hemoragic conditions, in 1910, platelets received a continuous attention, giving their roles in hemoastazis, coagulation, and wound repair. There are four different catheories of blood preparation, L-PRP being by far the most available, easy to use and, consequently, studied. The regenerative action of platelets concentrate is based on the growth factors from the intracellular granules, associated with soma plasmatic bioactive proteins. There are also other presumed effects of PRP, analgesic and anti-inflammatory, that necessitate further documentation. Studies revealed a clear regenerative action when injected intraarticular into the osteoarthritic knee. Other conditions that respond to PRP local administration are some tendinopathies, like tennis elbow and ”harvesting” patellar tendinopathy. Surgery for ligament reconstruction or nerve suture, in the presence of PRP, offered better outcomes. Discogenic low-back pain was treated with intradiscal PRP and showed promise as for reducing recurrence and improving function.

KEYWORDS: Platelet rich plasma, Tendinopathies, Surgery reconstruction.

INTRODUCTION
First use of platelets was documented in hemorrhagic disorders. William Duke, in 1910, proved that bleeding was provoked by thrombocytopenia and treatable with whole fresh blood transfusion, procedure that reversed the decreased number of platelets. Since then, platelets received increasing attention, starting with platelet concentrate for thrombocytopenic conditions and ending with the various types of platelet rich plasma for wound healing.

In the present day medicine, platelets are used in different domains of health, from orthopedic, surgery, dermatology, aesthetic medicine and dentistry. Their utility is sustained by the discovery of different factors that reside inside platelets.

In 2009, Ehrenfest[1,2] proposed a classification of four types of PRP products, according to cell content
Pure Platelet-Rich Plasma, P-PRP, is a leucocyte-poor product with high density of platelets and low-density fibrin network after activation.

Leucocyte- and PRP, L-PRP, contains platelets, leucocytes and low-density fibrin network after activation; this category is largely available, easy to use.

Pure Platelet-Rich Fibrin, P-PRF, contains no leucocytes, a high density of platelets and a high-density fibrin network; they have special recommendation to use.

Leucocyte- and Platelet-Rich Fibrin (L-PRF) are second-generation PRP and contains leucocytes and a high density-fibrin network.

We will refer in our review on the second category, as it is highly available and studied.

L-PRP without activation is injected immediately after preparation and the effect is local. Platelets slowly release their content from granules through exocytosis during several days.[3]
The components are platelets, leucocytes and plasma.

Circulating platelets count 150 – 400 x 10^3/μL, in PRP they count around 1000 x 10^3/μL; lower concentrations are impotent and higher concentrations may be harmful. Platelets are activated by endogenous and exogenous factors. Activation means exocytosis and degranulation. Platelets contains many types of granules. Alpha granules contain various types of bioactive molecules: clotting factors, fibrinolytic factors, membrane glycoproteins and growth factors (GF).[4,5] The most

seven known GF are PDGF (platelet-derived growth factor), TGF-β (transforming-growth factor beta 1, 2 and 3), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF), connective tissue growth factor (CTGF), insulin like growth factor 1 (IGF-1).[6,7] Additional GF are platelet-derived angiogenesis factor (PDAF), platelet factor 4 (PF-4), epithelial cell grow factor (ECGF), others cytokines. Growth factors bind to transmembrane receptors of target cells and regulate different pathways.[8] Target cells are mesenchymal stem cells, fibroblasts, osteoblasts, epidermal cells, endothelial cells.

Plasma contains three proteins: fibrin, fibronectin and vitronectin, which play in important role in cell adhesion[9] and other biologically active proteins: growth factor IGF-I and hepatocyte growth factor (HGF).

These regulated pathways promotes the expression of gene sequences that activate cellular proliferation, osteoid production, matrix formation, collagen synthesis. These processes lead to cell migration, proliferation and differentiation, angiogenesis, modulation of coagulation, vascular repair. The final process is tissue repair and regeneration.[10]

The role of the GF in PRP was studied in various situation. First, most GF were studied independently, on an individual use, rather than in the combination, as they exists in PRP. The separate molecules were followed in animal models. Second, the natural combination of all the GF from platelets together with plasma components were analyzed in animal and human models.

In fracture healing, PDGF promotes osteoblast migration through chemotaxis, as the cell express a PDGF-receptor. Blocking the activity of PDGF with an antibody results in blocking the osteoblast migration and, consequently, delaying the callus formation.[11]

TGF-β is a superfamily of GF that regulates cell proliferation, differention and growth. From this group, three potent members were investigated: TGF-β1, bone morphogenetic protein-2 (BMP-2), and BMP-7 (also known as osteogenic protein-1 [OP-1]).

Alongside with PDGF, they promote expression of collagen and cartilage matrix protein.[12] TGF-β influence fibroblasts, endothelial cells, preosteoblasts; thus increases angiogenesis and chondrogenesis and stimulates connective tissue production of fibronectin, glycosaminoglycans and collagen.[13] It sustains long-term healing and bone regeneration. A first study, from 1990, revealed the stimulative effects on new bone formation when injected subperiosteally in rat femur.[14] The expression of TGF-1 was higher in the PRP-treated rat Achilles tendon than in control, the result being a tendon with more rapid healing and better mechanical properties.

On the chondrocytes, TGF-β1 activates synthesis and reduces catabolic activity of IL-1,[15] accelerating cartilage defect repair.[16] In some studies, deleterious effects of TGF-β1 were noted: synovial proliferation, fibrosis and inflammation, osteophyte formation.

BMP-7 / OP-1 seems to be the gold standard GF for cartilage repair, as it increases anabolism and reduces catabolic activity of cytokines.[17] BMP-7 activity is not affected by the age of osteoarthritis,[18] unlike other chondrogenic GF.

BMP-7 acts synergic ally with insulin-like growing factor 1 (IGF-1), a molecule that is found the plasma component of PRP. IGF-1 has the same anabolic properties on cartilage, reducing the catabolic activity of lytic agents, but its action on ageing cartilage is diminished.[19]

VEGF is known to regulate vascular function and angiogenesis. Animal model studies revealed that prolonged and repetitive mechanic stress applied to tendons (particularly Achilles tendon) lead to high amount of VEGF production by the outer regions of the tendon.[20] This was considered a protective and repairing mechanism. As vascular hyperplasia is a characteristic feature of tendinosis, it is assumed that VEGF may have a central role in tendinosis pathogenesis. Exposing the rats Achilles tendon to VEGF-111 (a biologically active form of VEGF-A) post surgery accelerates healing. In the same direction, using VEGF-165 (another form of this GF) in an allograft reconstruction of rat anterior cruciate ligament improved revascularization, augmented mechanical properties and reduced recovery period.[21] There are also controversies around VEGF, as some researchers reported negative effect on tendon healing by means of vascular network formation in detriment of collagen network and by decreasing the mechanical properties of the tendon.[22,23]

Basic fibroblast growth factor (bFGF) is present in the cartilage matrix. Animal model studies revealed the reversal of osteoarthritic changes secondary to overload under bFGF administration[24] with an anabolic activity on chondrocytes. Controversy exists on its role within the cartilage, as researchers reported synovial inflammation and osteophyte formation when injecting intraarticular the factor alone.[25,26] The use of bFGF alone, as a synthetic product, is questionable, since it has deleterious effects on cartilage.

On an individual basis, GF may have positive and negative effects on the connective tissue. The natural activation sequence and quantitative rapport between these known factors and other factors not entirely studied is responsible for the regenerative effect of PRP. There is also another mechanic advantage of PRP, as it forms a three-dimensional network which fills the cartilage defect and promotes the neochondrogenesis.

Cartilage exposed to PRP showed increased cell proliferation and extracellular matrix synthesis. In the same time, synoviocytes exposed to PRP increased hyaluronic acid production. The combined action favors cartilage repair, protection and lubrication.[27]

In addition to the anabolic mechanism, there are other two presumed effects of PRP on the joint: analgesic and anti-inflammatory. There may be a direct analgesic effect of PRP, by augmenting cannabinoid receptors CB1 and CB2.[28] The anti-inflammatory activity may be due to inhibition of the nuclear factor-kB (Nf-kB) pathway.[29] Reducing inflammation might be more important for leucocyte-poor PRP than for leucocyte-rich PRP.[30] The subject requires further research.

Clinical studies are inhomogeneous; there is no standardized method for obtaining PRP, the concentration of platelets may differ according to original whole blood composition and to other physiologic factors (moment of the day, hydration status, lipid ingestion etc.).

A recent study[31] (published 2019) on a adequate sample size of patients, compared the result of three weekly intraarticular injections (knee) of PRP, hyaluronic acid (HA) and normal saline (NS)(control). At one month, all three groups showed improvement of WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score and of IKDC score (International Knee Documentation Committee - a subjective knee evaluation form), an unexpected result, which might be the result of a placebo effect. The 2, 6 and 12 months′ evaluation showed a significant improvement of objective and subjective knee evaluation for PRP group, with no improvement for the HA and NS groups.

Debate exists regarding the influence of patient age, severity of knee osteoarthritis, BMI and gender on the PRP results.

The American Academy of Orthopedic Surgeons admits that" treatment with PRP could hold promise", that the risks are minimal, equal to cortisone intra-articular injections.

As for Achilles tendon rupture, studies are debating on the utility of PRP use. Open surgical repair of the tendon associated with intraoperatory administration of PRP led to better results concerning the healing time, local complication and the risk of rerupture.[32] Another study revealed no difference between tendon surgery with PRP and without PRP regarding the biomechanical properties of tendon (maximum height with the Squat Jump test and maximum height with the Counter Movement Jump).[33]

Based on the encouraging results in animal models,[34] PRP was used for graft augmentation in anterior cruciate ligament reconstruction. When the donor site is the patellar tendon, PRP assures better healing.[35] For the graft maturation process, adding PRP intraoperatory accelerates and improves it.[36]

The category of tendinopathies, more recently known as tendinosis, lies on the morphologic aspect of degeneration rather than inflammation, hence the poor results on cortisone injections. PRP was thought to address the degenerative and vascular changes. For tennis elbow (lateral epicondylitis), PRP offered better result comparative with local anesthetic[37] (lidocaine), cortisone[38] and autologous blood.[39] In all studies local treatment was part of a complex rehabilitation program, centered on physical therapy.

For patellar tendinopathy PRP injection into the defect, together with a training program, improved algo-functional parameters.[40] It is important to note that most studies were done on severe and refractory patellar tendinopathies.[41]

Less encouraging results offered PRP on Achilles tendinopathy. Similar results were reported after PRP or saline injection, followed by physical exercise.[42] Sonographic evaluation revealed no difference between two treatments.[43]

Plantar fasciitis, especially refractory cases, are subject to local infiltration, cortisone or PRP, as part of rehabilitation program. For short-term (2 – 4 weeks) and intermediate-term (4 – 8 weeks), there were no differences between corticosteroid and PRP. For long-term, PRP was superior in pain suppression. Long-term effect of PRP and the potential deleterious effect on local cortisone may recommend PRP as a preferred treatment.[44]

The regeneration effect of PRP was used in reparative nerve surgery. The animal model studies promises a better outcome in the facial transected nerves, sutured and treated locally with PRP.[45] The conduction studies revealed better functional outcome when PRP was injected into the suture place.[46] Neurorrhaphy is essential for nerve continuity and is not replaceable by PRP administration, but the latter could accelerate repairment.[47]

Chronic discogenic low back pain has, as morpho pathogenic changes, intervertebral disc degeneration. In 2011 a study focused on PRP intervention on lumbar disc disease,[48] a group of 6 patients received one injection of PRP into the center of lumbar disc and reported the procedure was safe and improved pain and functional scores at one month, with persistence at 6 months follow-up. Since then, a few studies followed this line of treatment, reporting good clinical outcome. Only one randomized double-blind study[49] found statistically significant improvement in pain score and functional scales (Functional Rating Index FRI, Numeric Rating Scale NRS-best pain, the Short Form SF-36, modified

North American Spine Society NASS) at 6 weeks after treatment, with persistence after one year.

The therapy needs standardization, as the number and interval of injections, the method of obtaining PRP, the possible association with cell therapy, the place in the management of low back pain.

CONCLUSION

Intra-articular use of PRP in osteoarthritis is safe, with minimal risk and may be an option together with other therapies. PRP is most effective in the treatment of chronic tendon injuries, especially tennis elbow.[50] Promise exists for other chronic tendon lesions (Patellar and Achilles). Further studies will explain the mechanism of action and will establish clear indications.

REFERENCES

1. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF).Trends Biotechnol, 2009; 27(3): 158-67.
2. Dohan Ehrenfest DM, Bielecki T, Mishra A, Borzini P, Inchingolo F, Sammartino G, Rasmusson L, Everts PA, In search of a consensus terminology in the field of platelet concentrates for surgical use: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes.Curr Pharm Biotechnol, 2012; 13(7): 1131-7.
3. Lubkowska A, Dołęgowska B, Banfi G. growth factor content in PRP and their applicability in medicine. Journal of Biological Regulators & Homeostatic Agents, 2012; 26(2): 0-0.
4. Boswell, S. G., Cole, B. J., Sundman, E. A., Karas, V., & Fortier, L. A. Platelet-Rich Plasma: A Milieu of Bioactive Factors. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 2012; 28(3): 429–439.
5. Blair P, Flaumenhaft R. Platelet alpha-granules: Basic biology and clinical correlates. Blood Rev, 2009; 23: 177-189.
6. Sunitha Raja V, Munirathnam Naidu E.Platelet-rich fibrin: evolution of a second-generation platelet concentrate. Indian J Dent Re, 2008; 19(1): 42-6.
7. Maynard DM, Heijnen HF, Horne MK, White JG, Gahl WA. Proteomic analysis of platelet alpha-granules using mass spectrometry. J Thromb Haemost, 2007; 5: 1945-1955.
8. 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: 2259-2272.
9. 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.
10. Marx RE.Platelet-rich plasma: evidence to support its use.J Oral Maxillofac Surg, 2004; 62(4): 489-96.
11. Casati L, Celotti F, Negri-Cesi P, Sacchi MC, Castano P, Colciago A.Platelet derived growth factor (PDGF) contained in Platelet Rich Plasma (PRP) stimulates migration of osteoblasts by reorganizing actin cytoskeleton, Cell Adhesion & Migration, 2014; 8(6): 595-602
12. Lyras DN, Kazakos K, Tryfonidis M, Agrogiannis G, Botaitis S, Kokka A, Drosos G, Tilkeridis K, Verettas D. Temporal and spatial expression of TGF-beta1 in an Achilles tendon section model after application of platelet-rich plasma. Foot Ankle Surg, 2010; 16(3): 137–141.
13. Rudkin GH, Miller TA. Growth factors in surgery: Review. J Plastic Reconstr Surg, 1996; 97: 469-76.
14. Joyce ME, Roberts AB, Sporn MB, Bolander ME. Transforming growth factor-beta and the initiation of chondrogenesis and osteogenesis in the rat femur. J Cell Biol, 1990; 110(6): 2195–2207.
15. Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF-beta and osteoarthritis. Osteoarthritis Cartilage, 2007; 15: 597–604.
16. Diao H, Wang J, Shen C, Xia S, Guo T, Dong L, Zhang C, Chen J, Zhao J, Zhang J. Improved cartilage regeneration utilizing mesenchymal stem cells in TGF-beta1 gene-activated scaffolds. Tissue Eng Part A, 2009; 15: 2687–2698.
17. Chubinskaya S, Hurtig M, Rueger DC. OP-1/BMP-7 in cartilage repair. Int Orthop, 2007; 31: 773–781.
18. Merrihew C, Kumar B, Heretis K, Rueger DC, Kuettner KE, Chubinskaya S. Alterations in endogenous osteogenic protein-1 with degeneration of human articular cartilage. J Orthop Res, 2003; 21: 899–907.
19. Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet, 2010; 376: 440– 448.
20. Nakama LH, King KB, Abrahamsson S, Rempel DM. EGF, VEGFR-1, and CTGF cell densities in tendon are increased with cyclical loading: An in vivo tendinopathy model. J Orthop Res, 2006; 24(3): 393-400.
21. Chen J, Yang L, Guo L, Duan X. Sodium hyaluronate as a drug-release system for VEGF 165 improves graft revascularization in anterior cruciate ligament reconstruction in a rabbit model. Exp Ther Med, 2012; 4(3): 430-43.
22. Hou Y, Mao Z, Wei X, Lin L, Chen L, Wang H, Fu X, Zhang J, Yu C. Effects of transforming growth factor-beta1 and vascular endothelial growth factor 165 gene transfer on Achilles tendon healing. Matrix Biol, 2009; 28(6): 324-35.
23. Sahin H, Tholema N, Petersen W, Raschke MJ, Stange R. Impaired biomechanical properties correlate with neoangiogenesis as well as VEGF and MMP-3 expression during rat patellar tendon healing. J Orthop Res, 2012; 30(12): 1952-7.
24. Ellman MB, An HS, Muddasani P, Im HJ. Biological impact of the fibroblast growth factor

family on articular cartilage and intervertebral disc homeostasis. Gene, 2008; 420: 82–89.
25. Miyakoshi N, Kobayashi M, Nozaka K, Okada K, Shimada Y, Itoi E. Effects of intraarticular administration of basic fibroblast growth factor with hyaluronic acid on osteochondral defects of the knee in rabbits. Arch Orthop Trauma Surg, 2005; 125: 683– 692.
26. Siebert CH, Miltner O, Weber M, Sopka S, Koch S, Niedhart C. Healing of osteochondral grafts in an ovine model under the influence of bFGF. Arthroscopy, 2003; 19: 182–187.
27. Anitua E, Sanchez M, Nurden AT, Zalduendo MM, de la Fuente M, Azofra J, Andia I. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology (Oxford), 2007; 46: 1769–1772.
28. Lee HR, Park KM, Joung YK, Park KD, Do SH (2012) Platelet-rich plasma loaded hydrogel scaffold enhances chondrogenic differentiation and maturation with up-regulation of CB1 and CB2. J Control Release, 2012, 10; 159(3): 332–337.
29. Bendinelli P, Matteucci E, Dogliotti G, et al. Molecular basis of antiinflammatory action of platelet rich plasma on human chondrocytes: mechanisms of NF-kB inhibition via HGF. J Cell Physiol, 2010; 225: 757-766.
30. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. J Bone Joint Surg Am, 2012; 94(19): e143(1-8).
31. Lin, K.-Y., Yang, C.-C., Hsu, C.-J., Yeh, M.-L., & Renn, J.-H. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 2019; 35(1): 106–117.
32. Sánchez, M., Anitua, E., Azofra, J., Andía, I., Padilla, S., & Mujika, I. Comparison of Surgically Repaired Achilles Tendon Tears Using Platelet-Rich Fibrin Matrices. The American Journal of Sports Medicine, 2007; 35(2): 245–251.
33. De Carli, A., Lanzetti, R. M., Ciompi, A., Lupariello, D., Vadalà, A., Argento, G, Vetrano, M. Can platelet-rich plasma have a role in Achilles tendon surgical repair? Knee Surgery, Sports Traumatology, Arthroscopy, 2015; 24(7): 2231–2237.
34. Xie X, Zhao S, Wu H et al., "Platelet-rich plasma enhances autograft revascularization and reinnervation in a dog model of anterior cruciate ligament reconstruction," Journal of Surgical Research, 2013; 183(1): 214–222.
35. Cervellin M, de Girolamo L, Bait C, Denti M, Volpi P, "Autologous platelet-rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: a randomized, controlled clinical study," Knee Surgery, Sports Traumatology, Arthroscopy, 2012; 20(1): 114–120.
36. Radice F, Yánez R, Gutiérrez V, Rosales J, Pinedo M, Coda S, "Comparison of magnetic resonance imaging findings in anterior cruciate ligament grafts with and without autologous platelet-derived growth factors," Arthroscopy, 2010; 26(1): 50–57.
37. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am J Sports Med, 2006; 34: 1774-1778.
38. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med, 2010; 38: 255-262.
39. 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: 2130-2134.
40. Filardo G, Kon E, Della Villa S et al. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop, 2010; 34: 909-915.
41. Gosens T, Den Oudsten BL, Fievez E, van 't Spijker P, Fievez A. Pain and activity levels before and after plateletrich plasma injection treatment of patellar tendinopathy : a prospective cohort study and the influence of previous treatments. Int Orthop, 2012; 36: 1941-6.
42. de Jonge S, de Vos RJ, Van Schie HT et al. One-year follow-up of a randomised controlled trial on added splinting to eccentric exercises in chronic midportion Achilles tendinopathy. Br J Sports Med, 2010; 44: 673-677.
43. de Vos RJ, Weir A, Tol JL et al. No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. Br J Sports Med, 2011; 45: 387-392.
44. Yang, W. Y., Han, Y. H., Cao, X. W., Pan, J. K., Zeng, L. F., Lin, J. T., & Liu, J. (). Platelet-rich plasma as a treatment for plantar fasciitis: A meta-analysis of randomized controlled trials. Medicine, 96(44), e8475
45. Farrag, T. Y., Lehar, M., Verhaegen, P., Carson, K. A., & Byrne, P. J. Effect of platelet rich plasma and fibrin sealant on facial nerve regeneration in a rat model. Laryngoscope, 2007; 117(1): 157–165.
46. Sariguney, Y., Yavuzer, R., Elmas, C.,Yenicesu, I., Bolay, H., & Atabay, K. Effect of platelet-rich plasma on peripheral nerve regeneration. Journal of Reconstructive Microsurgery, 2008; 24(3): 159–167.
47. Yu, W., Wang, J., & Yin, J. Platelet-Rich Plasma: A Promising Product for Treatment of Peripheral Nerve Regeneration After Nerve Injury. International Journal of Neuroscience, 2011; 121(4): 176–180.

48. Akeda K, Imanishi T, Ohishi K, et al. Intradiscal injection of autologous serum isolated from platelet-rich-plasma for the treatment of discogenic low back pain: preliminary prospective clinical trial: GP141. Spine: Affiliated Society Meeting Abstracts, 2011.
49. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. PM R, 2016; 8: 1-10.
50. https://orthoinfo.aaos.org/en/treatment/platelet-rich-plasma-prp/.