

## THE EFFICACY OF PLATELET-RICH PLASMA USE AS A TREATMENT FOR THE OSTEOARTHRITIS

Jekaterina Plaksina, Agris Ilgažs

Latvia University of Agriculture  
vetik272@gmail.com

### Abstract

Platelet-rich plasma (PRP) is an autologous concentrated cocktail of growth factors and inflammatory mediators, and has been considered to be potentially effective for cartilage repair. Animal clinical studies suggest that PRP is a promising treatment for cartilage injuries and relieving symptoms due to its three biological properties: an anabolic effect, enhancement of cartilage regeneration and inhibition of inflammation. The aim of this article is to analyze the available evidence on the clinical application of this biological approach to animals for the injective treatment of cartilage lesions and joint degeneration, and also to support the rationale for the use of platelet concentrates and to give indications on what to expect from intra-articular injections of platelet-rich plasma (PRP) in animals. This article is a summary of analytical research papers about the use of platelet-rich plasma as a treatment for the osteoarthritis. The intra-articular injections do not just target cartilage; instead, platelet-rich plasma might influence the entire joint environment, leading to clinical improvement. Many biological variables might influence the clinical outcome and have to be studied to optimize PRP injective treatment of cartilage degeneration and osteoarthritis.

**Key words:** platelet-rich plasma, osteoarthritis, cartilage.

### Introduction

A healthy joint requires a fine-tuned balance between molecular signals regulating homeostasis, damage, restoration, and remodelling. This balance is determined both at the level of single cells and the whole tissue architecture, and it also involves interactions among different tissues such as cartilage, bone, synovium, ligaments, tendons, and menisci (Lores, 2008). Different factors are able to impair the maintenance of homeostasis in a joint that has been damaged or strained, and they may progressively lead to osteoarthritis (Heijink *et al.*, 2012). Osteoarthritis (OA) is a progressively debilitating condition that is associated with pain and morbidity. It is associated with ageing, trauma or joint congenital development abnormalities (dysplasia) and most often affects the joints of the knees, elbows, hips. Several treatment modalities are available, involving both conservative and operative approaches. Non-operative management includes analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, opioids, cartilage protective agents (glucosamine and chondroitin as well as physiotherapy). When these treatments fail, more invasive surgical approaches can be attempted to restore the mechanical balance and the regeneration of the articular surface, although results are still controversial (Fortier, Hackett, & Cole, 2011).

The search for a minimally invasive solution to improve the status of the joint surface and allow a fast return to full activity is therefore highly desirable. In this landscape, a novel promising injective treatment is platelet-rich plasma (PRP), a blood derivative that has a higher platelet concentrate than whole blood. When activated, platelets release a group of biologically active proteins that bind to the transmembrane receptors of their target cells, thus leading to the

expression of gene sequences that ultimately promote cellular recruitment, growth, and morphogenesis, and modulating inflammation as well (Anitua, Sanchez, & Orive, 2010). Therefore, PRP represents an appealing biological approach to favour the healing of tissues with a low healing potential, such as cartilage. This led to the wide use of PRP, which shows promising results as a minimally invasive injective treatment of cartilage degeneration and OA, both in preclinical and clinical studies (Kon *et al.*, 2013).

The aim of this paper is to analyze the available evidence on the clinical application of this biological approach to animals for the injective treatment of cartilage lesions and joint degeneration and as well as to support the rationale for the use of platelet concentrates and to give indications on what to expect from intra-articular injections of platelet-rich plasma (PRP) in animals.

### Materials and Methods

Monographic method has been used for this article. As the research on use of platelet-rich plasma in veterinary medicine in Latvia is quite new, available scientific literature from other countries has been studied. All animal clinical trials on PRP injective treatment concerning the effect of PRP on cartilage, synovial tissue, and menisci were studied.

### Results and Discussion

Concerning the animal clinical studies dealing with PRP injective treatment, we found 18 papers: 6 on rabbits, 4 on dogs, 3 on rats, 3 on sheeps, 1 on horses, and 1 on pigs, which showed heterogeneous results for heterogeneous indications.

Seven papers focused on OA treatment. Contrasting results have been reported in the small

animal model. In fact, Guner & Buyukbebeci (2012) did not find any immediate (2 weeks after the injection cycle) benefit of PRP on cartilage tissue in rat joints previously damaged with intra-articular formalin injection. Mifune *et al.* (2013) found in a rat OA model, induced by monosodium iodoacetate injection, that PRP had no marked effect by itself, but increased the cartilage repair effect of muscle derived stem cells, with a better histologic appearance, higher number of cells producing type II collagen, and lower levels of chondrocyte apoptosis at 4 weeks, although at 12 weeks its effects were lost. Kwon, Park, & Lee (2012) confirmed the benefit of PRP in a rabbit model of collagenase-induced OA: intra-articular injections influenced positively the cartilage regeneration in all OA severity degrees, with a more evident effect in moderate OA. Fahie *et al.* (2013) found that a single intra-articular injection of an autologous platelet rich-plasma concentrate significantly improves lameness, pain and peak vertical force scores at 12 weeks in 20 dogs with OA involving a single joint. Cook *et al.* (2015) performed five PRP injections in canine knee joint where the anterior cruciate ligament (ACL) was particularly transected and menisci was released. PRP-treated knees showed evidence of repair and less severe synovitis, also improved range of motion, decreased pain, and improved limb function for up to 6 months compared to saline-treated joints. Saito *et al.* (2009) used a rabbit OA model of anterior cruciate ligament resection for the treatment with gelatin hydrogel microspheres impregnated with PRP: injections markedly suppressed OA progression both morphologically and histologically (less significant results were obtained by the use of PRP only). Finally, Carmona *et al.* (2007) used a large animal model to analyze the effect of PRP injections: in a study on 4 horses with OA, 3 injections of PRP led to a significant improvement in both the degree of lameness and joint effusion. The most marked improvement was observed 2 months after treatment and persisted for 8 months with no adverse events.

Eleven studies focused on the injective treatment of chondral, osteochondral and ligament lesions. Also in this case, results were controversial. Serra *et al.* (2013) performed 7 PRP injections every other day in rabbit joints where a full-thickness osteochondral lesion was previously made surgically on the medial femoral condyle. A fibrous–cartilaginous tissue was found with no benefit from PRP. Smyth *et al.* (2015) performed one PRP injection in a rabbit knee where osteochondral lesion was previously made. There was no significant difference in macroscopic scores between the two groups, but histologic results were better and also greater glycosaminoglycan and type II collagen content in the repair tissue. Lee *et al.* (2016) performed a full-thickness circular defect

on the menisci of rabbit filled with PRP. After eight weeks, the lesions in the control and PRP groups were occupied with fibrous tissue, but not with meniscal cells. PRP treatment of the meniscus results in an increase of catabolic molecules, especially those related to interleukin-1 $\alpha$  induced inflammation. Hapa *et al.* (2013) evaluated PRP as augmentation in rat cartilage lesions after microfractures: at week 6, the microfracture group score was worse than that of the PRP microfracture group, which had an increased degree of type II collagen staining. Wei *et al.* (2007) found that chondrocytes/PRP composites injected subcutaneously in rabbits after 2 months form a new cartilage. In contrast, no tissue formed in the PRP-alone group. So results suggest the feasibility of using PRP as injectable scaffold seeded with chondrocytes to regenerate cartilage and showed the potential of using this method for the reconstruction of cartilage defects. Milano *et al.* (2010) used one PRP injection as augmentation procedure of microfracture in a sheep model. Although no hyaline cartilage was obtained, PRP offered better macroscopic, histologic, and biomechanical results. The PRP administration modality proved to be important for the final outcome, with better results when PRP was surgically applied as a gel over the treated lesion. However, this required a more invasive approach. Thus, in a further evaluation in sheep, Milano *et al.* (2011, 2012) focused on the injective approach: 5 weekly injections of PRP promoted a better spontaneous repair and also a better and more durable reparative response when applied after microfractures with respect to isolated microfractures, albeit without producing hyaline cartilage. Murray *et al.* (2006) used collagen-PRP scaffold to treat a central anterior cruciate ligament (ACL) defect in 10 dogs. Biomechanically, the treated ACL defects had a 40% increase in strength at 6 weeks, which was significantly higher than the 14% increase in strength of untreated defects. Xie *et al.* (2013) observed the increased expression of vascular endothelial growth factor, neurotrophin-3, thrombospondin-1 and nerve growth factor in canine ACL grafts treated with PRP at 2, 6 and 12 weeks after surgery.

Finally, only 1 paper focused on rheumatoid arthritis (RA). Lippross *et al.* (2011) reproduced RA in pigs: the animals were systemically immunized by bovine serum albumin (BSA) injections, and arthritis was induced by intra-articular BSA injection. The injection of PRP attenuated the arthritic changes on synovium and cartilage by modulating the activity of inflammation mediators. In particular, interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) staining was reduced, but concerning gene expression, only IL-6 levels were significantly lower after PRP application. Focusing on protein quantification, all

chondral protein concentrations returned to healthy tissue levels, and in synovial samples, besides the low levels of IL-6 and VEGF, the authors showed a reduction in insulin-like growth factor (IGF-1) and interleukin-1 $\beta$  (IL-1 $\beta$ ) in PRP groups, whereas tumor necrosis factor $\alpha$  (TNF $\alpha$ ) was not altered. So they conclude that treatment with PRP led to attenuation of these arthritic changes in the synovium and cartilage.

This systematic review confirmed the increasing interest in PRP as an injective treatment for cartilage degeneration and osteoarthritis, with an increasing number of published studies over time. PRP is a fashionable treatment, offering the possibility to deliver a high concentration of autologous growth factors and bioactive molecules in physiologic proportions, with low costs and in a minimally invasive way. This explains the wide application of this blood derivative to several tissues and heterogeneous pathologies in different fields of medicine (Kon *et al.*, 2012). The rationale for using platelets for the treatment of different tissues is that they constitute a reservoir of growth factors that are critical for regulating the tissue healing process, which is quite similar in all kinds of tissues. However, even though the rationale for PRP use in other tissues is clear, since platelets represent the first response to a tissue damage where they participate in stopping the vessel bleeding and trigger the healing cascade (Cole *et al.*, 2010), less intuitive is the rationale for PRP use in cartilage, which is a physiologically vessel-free tissue. 123 molecules such as transforming growth factor beta might justify its use in cartilage; PRP also contains other molecules such as vascular endothelial growth factor that do not take part or might even jeopardize cartilage homeostasis and regeneration (Mifune *et al.*, 2013).

The systematic analysis of studies published up to now shows an overall positive effect of PRP on cartilage tissue. Besides some controversial results, most of the findings supported the role of PRP in increasing chondrocyte proliferation, without affecting chondrogenic phenotype and with an increase in the production of matrix molecules. Studies confirmed the usefulness of PRP treatment in different pathology models, with good results in cartilage regeneration after acute focal lesions, as well as in the more complex environment of joint osteoarthritic degeneration, and even in the challenging rheumatoid arthritis setting.

An intra-articular injection does not just target cartilage, instead, PRP might influence the entire joint environment, and some studies confirm the effects of PRP on other cell sources. Synoviocytes are affected by platelet releasate, as well as meniscal cells that seem to be induced by PRP and act synergically toward tissue healing. PRP has several potential effects by enhancing the cell signalling cascade in all joint tissues and inducing positive changes in the whole

joint environment through a milieu of actions. Among these, tissue regeneration is actually not the only and maybe not the most important PRP mechanism of action, and increasing evidence supports the complex role of PRP in modulating inflammation. An overall down-modulation of the joint inflammation can explain the well-documented pain reduction, which is the most prominent and disabling symptom of cartilage lesions and OA. However, some findings suggest another intriguing aspect of PRP action mechanism, with a direct analgesic effect: Lee *et al.* (2016) showed the role of PRP in the augmentation of cannabinoid receptors CB1 and CB2, which might be involved in the analgesic effects. Further studies need to focus on understanding and possibly optimizing the analgesic and anti-inflammatory effects of PRP. PRP might not lead to hyaline cartilage regeneration and might not change the clinical history with significant disease-modifying properties, but it still might offer a clinical benefit with symptoms and function improvement and possibly a slowdown of the degenerative processes. The central feature in OA cartilage degeneration is the so-called apoptosis (programmed cell death); thus, chondrocytes apoptosis is a potential therapeutic target for OA interventions. The exact mechanism behind the PRP regulation of the apoptotic pathway is unclear, but it is likely that PRP might have an overall effect in slowing down the apoptosis cascade.

PRP injections seem to be safe, as we did not find adverse events reported in animal studies. Many studies have a small animal group or amount of cases, thereby they are not representative. Therefore, more high-quality trials are required.

Several aspects still need to be studied to understand the mechanism of action of PRP and give better treatment indications, and possibly to optimise the procedure and improve the potential of this biological minimally invasive approach for the treatment of cartilage.

## Conclusions

Research findings derived from animal clinical studies suggest that PRP is a promising treatment for cartilage injuries and relieving symptoms due to its three biological properties. Firstly, PRP has an anabolic effect on chondrocytes and synoviocytes with resultant increases in cell proliferation and secretion of hyaluronic acid. Secondly, PRP may act as a bioactive cell scaffold to fill defects and enhance cartilage regeneration. Thirdly, PRP has the potential to inhibit inflammation and alleviate OA symptoms. Many biological variables might influence the clinical outcome and have to be studied to optimize PRP injective treatment of cartilage degeneration and osteoarthritis.

## References

1. Anitua, E., Sanchez, M., & Orive, G. (2010). Potential of endogenous regenerative technology for in situ regenerative medicine. *Advanced Drug Delivery Reviews*, 62 (7-8), 741-752. DOI: 10.1016/j.addr.2010.01.001.
2. Carmona, J.U., Arguelles, D., Climent, F., & Prades, M. (2007). Autologous platelet concentrates as a treatment of horses with osteoarthritis: a preliminary pilot clinical study. *Journal of Equine Veterinary Science*, 27(4), 167-170. DOI: 10.1016/j.jevs.2007.02.007.
3. Cole, B.J., Seroyer, S.T., Filardo, G., Bajaj, S., & Fortier, L.A. (2010). Platelet-rich plasma: where are we now and where are we going? *Sports Health*, 2(3), 203-210. DOI: 10.1177/1941738110366385.
4. Cook, J.L., Smith, P.A., Bozynski, C.C., Kuroki, K., Cook, C.R., Stoker, A.M., & Pfeiffer, F.M. (2015). Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. *Journal of Orthopaedic Research*, 24(4), 820-830. DOI: 10.1002/jor.23054.
5. Fahie, M.A., Ortolano, G.A., Guercio, V., Schaffer, J.A., Johnston, G., Au, J., Hettlich, B.A., Phillips, T., Allen, M.J., & Bertone, A.L. (2013). A randomized controlled trial of the efficacy of autologous platelet therapy for the treatment of osteoarthritis in dogs. *Journal of the American Veterinary Medical Association*, 243(9), 1291-1297. DOI: 10.2460/javma.243.9.1291.
6. Fortier, L.A., Hackett, C.H., & Cole, B.J. (2011). The Effects of Platelet-Rich Plasma on Cartilage: Basic Science and Clinical Application. *Operative Techniques in Sports Medicine*, 19(3), 154-159. DOI: 10.1053/j.otsm.2011.03.004.
7. Guner, S., & Buyukbeci, O. (2012). Analyzing the effects of platelet gel on knee osteoarthritis in the rat model. *Clinical and Applied Thrombosis/Hemostasis*, 19(5), 494-498. DOI: 10.1177/1076029612452117.
8. Hapa, O., Cakici, H., Yuksel, H.Y., Fırat, T., Kukner, A., & Aygun, H. (2013). Does platelet-rich plasma enhance microfracture treatment for chronic focal chondral defects? An in vivo study performed in a rat model. *Acta Orthopaedica et Traumatologica Turcica*, 47(3), 201-207. DOI: 10.3944/AOTT.2013.2928.
9. Heijink, A., Gomoll, A.H., Madry, H., Drobnic, M., Filardo, G., Espregueira-Mendes, J., & Van Dijk, C.N. (2012). Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. *Knee Surgery, Sports Traumatology, Arthroscopy*, 20(3), 423-435. DOI: 10.1007/s00167-011-1818-0.
10. Kon, E., Filardo, G., Matteo, B.D., & Maccacci, M. (2013). PRP for the treatment of cartilage pathology. *Open Orthopedic Journal*, 3(7), 120-128. DOI: 10.2174/1874325001307010120.
11. Kon, E., Filardo, G., Drobnic, M., Madry, H., Jelic, M., van Dijk, N., & Della Villa, S. (2012). Non-surgical management of early knee osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, 20(3), 436-449. DOI: 10.1007/s0016701117138.
12. Kwon, D.R., Park, G.Y., & Lee, S.U. (2012). The effects of intra-articular platelet-rich plasma injection according to the severity of collagenase-induced knee osteoarthritis in a rabbit model. *Annals of Rehabilitation Medicine*, 36, 458-465. DOI: 10.5535/arm.2012.36.4.458.
13. Lee, H.R., Shon, O.J., Park, S.I., Kim, H.J., Kim, S., Ahn, M.W., & Do, S.H. (2016). Platelet-rich plasma increases the levels of catabolic molecules and cellular dedifferentiation in the meniscus of a rabbit model. *International Journal of Molecular Sciences*, 17(1), 120. DOI: 10.3390/ijms17010120.
14. Lippross, S., Moeller, B., Haas, H., Tohidnezhad, M., Steubesand, N., Wruck, C.J., Kurz, B., Seekamp, A., Pufe, T., & Varoga, D. (2011). Intraarticular injection of platelet-rich plasma reduces inflammation in a pig model of rheumatoid arthritis of the knee joint. *Arthritis & Rheumatology*, 63(11), 3344-3353. DOI: 10.1002/art.30547.
15. Lories, R.J. (2008). Joint homeostasis, restoration, and remodeling in osteoarthritis. *Best Practice & Research Clinical Rheumatology*, 22(2), 209-220. DOI: 10.1016/j.berh.2007.12.001.
16. Mifune, Y., Matsumoto, T., Takayama, K., Ota, S., Li, H., Meszaros, L.B., Usas, A., Nagamune, K., Gharaibeh, B., Fu, F.H., & Huard, J. (2013). The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair. *Osteoarthritis and Cartilage*, 21, 175-185. DOI: 10.1016/j.joca.2012.09.018.
17. Milano, G., Deriu, L., Sanna Passino, E., Masala, G., Manunta, A., Postacchini, R., Saccomanno, M.F., & Fabbriani, C. (2012). Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral defects of the knee: an experimental study in an animal model. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, 28(5), 688-701. DOI: 10.1016/j.arthro.2011.09.016.
18. Milano, G., Deriu, L., Sanna Passino, E., Masala, G., Saccomanno, M.F., Postacchini, R., & Fabbriani, C. (2011). The effect of autologous conditioned plasma on the treatment of focal chondral defects of the

- knee. An experimental study. *International Journal of Immunopathology & Pharmacology*, 24, 117-124. DOI: 10.1177/03946320110241S222.
19. Milano, G., Sanna Passino, E., Deriu, L., Careddu, G., Manunta, L., Manunta, A., Saccomanno, M.F., & Fabbriciani, C. (2010). The effect of platelet rich plasma combined with microfractures on the treatment of chondral defects: an experimental study in a sheep model. *Osteoarthritis and Cartilage*, 18(7), 971-980. DOI: 10.1016/j.joca.2010.03.013.
  20. Murray, M.M., Spindler, K.P., Devin, C., Snyder, B.S., Muller, J., Takahashi, M., Ballard, P., Nanney, L.B., & Zurakowski, D. (2006). Use of a collagen-platelet rich plasma scaffold to stimulate healing of a central defect in the canine ACL. *Journal of Orthopaedic Research*, 24(4), 820-830. DOI: 10.1002/jor.20073.
  21. Saito, M., Takahashi, K.A., Arai, Y., Inoue, A., Sakao, K., Tonomura, H., Honjo, K., Nakagawa, S., Inoue, H., Tabata, Y., & Kubo, T. (2009). Intraarticular administration of platelet-rich plasma with biodegradable gelatin hydrogel microspheres prevents osteoarthritis progression in the rabbit knee. *Clinical and Experimental Rheumatology*, 27 (2), 201-207.
  22. Serra, C.I., Soler, C., Carillo, J.M., Sopena, J.J., Redondo, J.I., & Cugat, R. (2013). Effect of autologous platelet-rich plasma on the repair of full-thickness articular defects in rabbits. *Knee Surgery, Sports Traumatology, Arthroscopy*, 21(8), 1730-1736. DOI: 10.1007/s0016701221410.
  23. Smyth, N.A., Haleem, A.M., Ross, K.A., Hannon, C.P., Murawski, C.D., Do, H.T., & Kennedy, J.G. (2015). Platelet-rich plasma may improve osteochondral donor site healing in a rabbit model. *Cartilage*, 7(1), 104-111. DOI: 10.1177/1947603515599190.
  24. Wei, W., Fulin, C., Yanpu, L., Qui, M., & Tianqiu, M. (2007). Autologous injectable tissue engineered cartilage by using platelet-rich plasma: experimental study in a rabbit model. *Journal of Oral Maxillofacial Surgery*, 65(10), 1951-1957. DOI: 10.1016/j.joms.2006.11.044.
  25. Xie, X., Zhao, S., Wu, H., Xie, G., Huangfu, X., He, Y., & Zhao, J. (2013). Platelet-rich plasma enhances autograft revascularization and reinnervation in a dog model of anterior cruciate ligament reconstruction. *Journal of Surgical Research*, 183(1), 214-222. DOI: 10.1016/j.jss.2013.01.020.