



Editorial

Interventional Orthobiologics a ray of hope

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1. Introduction

The revivification of regenerative medicine based on known bio-scientific principles addresses the major challenges to human health, specifically in the branch of orthopaedics.¹ Various strategies have been implicated to augment the healing potential of the affected tissue,² it includes prolotherapy, viscosupplementation, platelet-rich plasma (PRP), and autologous mesenchymal stem cells (MSCs), culture-based MSCs and the acellular MSCs derived nano molecule called as exosomes (MSCs-Exos). Here we have a short review of the nature of these biologicals and their applications.

2. Operational Principles of Orthobiologic Procedures

The sequential biological process of any interventional orthobiologic procedure includes controlled inflammation, differentiation (when MSCs used), proliferation (when PRP is used), maturation and regeneration³ as shown in Figure 1.

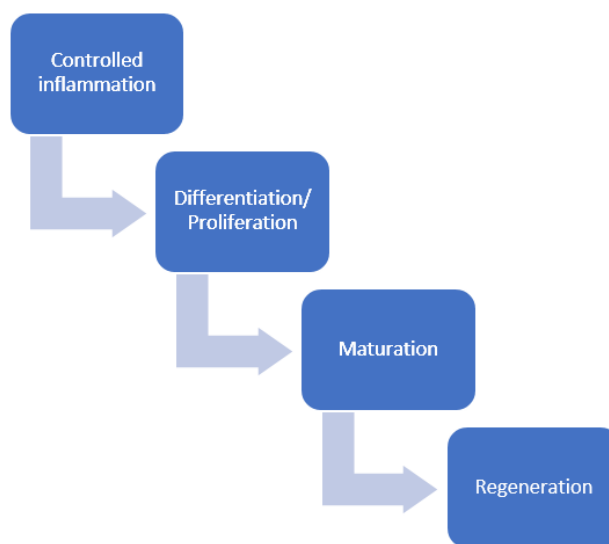


Fig. 1: Working principles of any procedural orthobiologics.

3. Various Sources of Biological Therapy

3.1. Platelet-rich plasma

Platelet-rich plasma with a cargo of the biologically active differential growth factors within the α granules

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plays a crucial role in tissue healing and regeneration.⁴ This autologous conditioned plasma has been categorized into four types based on leukocyte and fibrin content: (i) leukocyte rich PRP (L-PRP), (ii) leukocyte depleted pure PRP (P-PRP), (iii) leukocyte platelet-rich fibrin (L-PRF), and (iv) leukocyte depleted pure platelet-rich fibrin (P-PRF). The breakdown of α granules facilitates controlled activation of neutrophils, which initiates the recruitment and differentiation of various cell types at the desired site. This combined activation of thrombocytes, platelets and macrophages (M1 and M2 plasticity) mediates “regenerative inflammation”.⁵

Platelet Lysate therapy has been shown to enhance neural tissue regeneration in patients with peripheral neuropathy⁶ and nerve injuries.⁷ However, PRP works well by altering the articular microenvironment in the early phase of degeneration but it does not alter the degenerated joint.⁸

3.2. Mesenchymal Stem Cells (functionally- Messenger Signalling Cells)

The autologous MSCs are generally derived from adipose tissue, adipose stromal vascular fraction (SVF), bone marrow, synovial tissue and pericytes (perivascular, perichondral, periosteal and dental pulp) whereas the allogenic culture-expanded stem cells are derived from placenta, amniotic membrane, embryonic tissues, Wharton’s jelly and umbilical cord. Because of their pluripotency, MSC lineages have been used for bone, cartilage and epithelial regeneration⁹.

4. Clinical Applications

4.1. Tendinopathy

OI therapy has shown efficacy in treating chronic lateral epicondylitis¹⁰, rotator cuff¹¹, Achilles¹² and patellar tendinopathy¹³ when compared to corticosteroids in the previous studies¹⁴.

4.2. Degenerative bone and joint disease

Various clinical studies have shown good results for conditions like osteoarthritis,¹⁵ degenerative disc disease, and lumbar radiculopathy.¹⁶

4.3. Inflammatory bone and joint disease

In recent years, the immunomodulatory properties of mesenchymal stem cells have been well utilized for the treatment of rheumatoid arthritis¹⁷ and even for certain seronegative conditions like ankylosing spondylitis, psoriatic arthropathy.

4.4. Focal chondral defect and meniscal repair

Advanced regenerative techniques have shown an ability to enhance cartilage regeneration. The composition, quality

and durability of the newly formed cartilage are highly comparable to that of naïve cartilage.¹⁸

4.5. Fracture healing and avascular necrosis

Various studies show that regenerative therapies have been well implicated in the management of delayed union and certain cases of established non-union with good results.¹⁹ Recently, it has been evaluated that the BMAC and the cultured osteoblasts therapies have shown excellent short-term results in the early stages of avascular necrosis of the femoral head.²⁰

5. Conclusion

Interventional orthobiologics as an emerging branch has a long way to go to develop consensus regarding the therapeutic benefits, the types of procedures, the disease-specific dose standardization and the legal concerns related to such procedures. Such recommendations need to be formulated to understand the limitations of these time points to enhance the healing potential and tissue regeneration.

6. Conflict of Interest


None.


References


1. Rand E, Gellhorn AC. The Healing Cascade: Facilitating and Optimizing the System. *Phys Med Rehabil Clin N Am*. 2016;27(4):765–81. doi:10.1016/j.pmr.2016.07.001.
2. Centeno CJ, Pastoriza SM. Past, Current And Future Interventional Orthobiologics Techniques and How They Relate To Regenerative Rehabilitation: A Clinical Commentary. *Int J Sports Phys Ther*. 2020;15(2):301–25.
3. Liu SH, Yang RS, Shaikh R, Lane JM. Collagen in tendon, ligament, and bone healing. A current review. *Clin Orthop Relat Res*. 1995;(318):265–78.
4. Lana JF, Huber SC, Purita J, Tambeli CH, Santos GS, Paulus C, et al. Leukocyte-rich PRP versus leukocyte-poor PRP - The role of monocyte/macrophage function in the healing cascade. *J Clin Orthop Trauma*. 2019;10(1):S7–12. doi:10.1016/j.jcot.2019.05.008.
5. Uchiyama R, Toyoda E, Maehara M, Wasai S, Omura H, Watanabe M, et al. Effect of Platelet-Rich Plasma on M1/M2 Macrophage Polarization. *Int J Mol Sci*. 2021;22(5):2336. doi:10.3390/ijms22052336.
6. Anjayani S, Wirohadidjojo YW, Adam AM, Suwandi D, Seweng A, Amiruddin MD, et al. Sensory improvement of leprosy peripheral neuropathy in patients treated with perineural injection of platelet-rich plasma. *Int J Dermatol*. 2013;53(1):109–13. doi:10.1111/ijd.12162.
7. Kuffler DP, Reyes O, Sosa JJ, Santiago-Figueroa J. Neurological recovery across a 12-cm-long ulnar nerve gap repaired 3.25 years post trauma: case report. *Neurosurgery*. 2011;69(6):1321–6. doi:10.1227/NEU.0b013e31822a9fd2.
8. Kennedy MI, Whitney K, Evans T, Laprade RF. Platelet-Rich Plasma and Cartilage Repair. *Curr Rev Musculoskelet Med*. 2018;11(4):573–82. doi:10.1007/s12178-018-9516-x.
9. Caplan AI. Mesenchymal Stem Cells: Time to Change the Name! *Stem Cells Transl Med*. 2017;6(6):1445–51. doi:10.1002/sctm.17-0051.
10. Gosens T, Peerbooms JC, Van Laar W, Oudsten BD. 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. doi:10.1177/0363546510397173.
11. Gumina S, Campagna V, Ferrazza G, Giannicola G, Fratalocchi F, Milani A, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. *J Bone Joint Surg Am.* 2012;94(15):1345–52. doi:10.2106/JBJS.K.00394.
 12. Deans VM, Miller A, Ramos J. A prospective series of patients with chronic Achilles tendinopathy treated with autologous-conditioned plasma injections combined with exercise and therapeutic ultrasonography. *J Foot Ankle Surg.* 2012;51(6):706–10. doi:10.1053/j.jfas.2012.06.009.
 13. Charousset C, Zaoui A, Bellaiche L, Bouyer B. Are multiple platelet-rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes? a prospective study. *Am J Sports Med.* 2014;42(4):906–11. doi:10.1177/0363546513519964.
 14. Paredes JJ, Andarawis-Puri N. Therapeutics for tendon regeneration: a multidisciplinary review of tendon research for improved healing. *Ann N Y Acad Sci.* 2016;1383(1):125–38. doi:10.1111/nyas.13228.
 15. Laver L, Marom N, Dnyanesh L, Mei-Dan O, Espregueira-Mendes J, Gobbi A, et al. PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. *Cartilage.* 2016;8(4):341–64. doi:10.1177/1947603516670709.
 16. Centeno C, Markle J, Dodson E, Stemper I, Hyzy M, Williams C, et al. The use of lumbar epidural injection of platelet lysate for treatment of radicular pain. *J Exp Orthop.* 2017;4(1):38. doi:10.1186/s40634-017-0113-5.
 17. Luque-Campos N, Contreras-López RA, Paredes-Martínez MJ, Torres MJ, Bahraoui S, Wei M, et al. Mesenchymal Stem Cells Improve Rheumatoid Arthritis Progression by Controlling Memory T Cell Response. *Front Immunol.* 2019;10:798. doi:10.3389/fimmu.2019.00798.
 18. Venosa M, Calafiore F, Mazzoleni M, Romanini E, Cerciello S, Calvisi V, et al. Platelet-Rich Plasma and Adipose-Derived Mesenchymal Stem Cells in Association with Arthroscopic Microfracture of Knee Articular Cartilage Defects: A Pilot Randomized Controlled Trial. *Adv Orthop.* 2022;p. 6048477. doi:10.1155/2022/6048477.
 19. Campbell WC. Delayed union and nonunion of fractures." Chapter 15 ; 1939.
 20. Hernigou P, Daltro G, Hernigou J. Hip osteonecrosis: stem cells for life or behead and arthroplasty? *Int Orthop.* 2018;42(7):1425–8. doi:10.1007/s00264-018-4026-4.

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