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CHRONIC PAIN MEDICINE (A ABD-ELSAYED, SECTION EDITOR)

Current Review of Regenerative Medicine Therapies for Spine-Related Pain

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Abstract

Purpose of Review Persistent spinal pain syndromes are pervasive and lead to functional impairment, increased healthcare utilization, potential disability, and high societal costs. Spinal (cervical, thoracic, lumbar, and sacroiliac joint) pain includes mechanical, degenerative, inflammatory, oncologic, and infectious etiologies. Regenerative medicine is a novel biotechnology targeting mechanical, degenerative, and inflammatory conditions believed to cause pain. Preparations including platelet-rich plasma, mesenchymal stem cells (adipose tissue and bone marrow aspirate concentrates), and growth factors are derived from an autologous donor. The goal of intervention through guided injection of the regenerative media is to reduce inflammation and reverse the degenerative cascade in hopes of restoring normal cellular composition (physiologic homeostasis) and anatomical function to improve pain and function. The authors review limited research supporting the use of platelet-rich plasma injections for facet joint arthropathy and sacroiliac joint pain compared to traditional steroid treatments, as well as the use of platelet rich plasma or mesenchymal stem cells for lumbar discogenic and radicular pain.

Recent Findings Current evidence to support regenerative medicine for spine-related pain is limited. Although several studies demonstrated a reduction in pain, many of these studies had a small number of participants and were case series or prospective trials.

Summary Regenerative medicine treatments lack evidence for the treatment of spine-related pain. Large randomized controlled trials are needed with consistent study protocols to make further recommendations.

Keywords Regenerative medicine · Platelet-rich plasma · Mesenchymal stem cells · Spine-related pain

Introduction

Regenerative medicine (RM) is an interdisciplinary specialty that aims at restoring diseased and/or damaged tissue by activating the body's natural growth and repair processes. RM has shown clinical success at treating varying maladies, including, but not limited to, dermal injuries, cardiovascular disease, and even certain types of cancer [1–4]. A newly emerging application of RM is for the treatment of chronic spine pain, specifically, addressing cervical and lumbar pain. Back pain, specifically low back pain, is a leading cause of pain and disability around the world, and it is estimated that by 2050, nearly 850 million individuals globally will suffer from chronic low back pain [5]. The application of RM shows promise at addressing the common etiologies of back pain by slowing or halting tissue and mechanical degeneration, downregulating inflammation, and restoring tissue integrity through the growth of healthy new tissue. RM utilizes numerous therapeutic strategies to achieve desirable clinical outcomes, such as growth factors, stem cells, platelet-rich plasma, and prolotherapy [6]. Compared with more traditional therapies, such as steroids, which only suppress inflammation, RM promises a more comprehensive solution.

However, with any emergent therapy, it is imperative to appropriately quantify, and qualify, outcomes to properly set patient expectations. The aim of this review is to highlight the multitude of regenerative therapies for the spine and help establish clinic outcomes based on current research and data available.

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Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous blood fraction composed of plasma with platelet concentrations five times higher than normal values [7, 8]. For more than 40 years, PRP therapies have been employed in several medical settings including orthopedics, interventional pain, dermatology, hematology, oral and maxillofacial surgery, and RM. The use of PRP has shown promising results, given the regenerative properties of its biologically active cellular components. These developments have offered new possibilities for treating and managing musculoskeletal and chronic degenerative pain conditions. While platelets are a relatively small component of blood, they are rich in growth factors. They play a critical role in forming blood clots during injuries and are crucial for the healing process of damaged tissues. An increased platelet count at the injury site (acute or chronic) leads to elevated secretion of growth factors and facilitating and accelerating the healing process [8]. PRP therapy functions by nurturing cells that facilitate self-healing or aid in the healing process of injured tissues [9].

Platelet involvement is crucial in the healing process of injured tissues. Platelets serve as reservoirs for protein-signaling molecules. Once these molecules are secreted at the site of tissue injury, they exert their effects on stem cells, fibroblasts, osteoblasts, endothelial cells, and epithelial cells. The seven known growth factors in PRP are platelet-derived growth factor aa (PDGFaa), PDGFbb, PDGFab, transforming growth factor beta-1 (TGF-b1), TGF-b2, vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF). The high concentration of platelets contained in PRP delivers an increased number of growth factors and signaling molecules to the treatment target, promoting cell proliferation of healing-capable cells and angiogenesis within the tissues [10, 11]. These growth factors play a central role in revascularizing damaged tissues by promoting cell migration, proliferation, differentiation, and stabilization of endothelial cells in newly formed blood vessels.

Furthermore, PRP contributes restoring damaged connective tissue through the migration, proliferation, and activation of fibroblasts [8, 12]. In addition to growth factors, chemokines and cytokines activate downstream cellular signaling pathways, leading to the synthesis of proteins necessary for collagen, osteoid, and extracellular matrix formation [13]. Additionally, PRP contains several cell adhesion molecules, including fibrin, fibronectin, vitronectin, and thrombospondin, facilitating the integration of osteoblasts, fibroblasts, and epithelial cells [8].

Mesenchymal Stem Cells (MSC)

Adipose-Derived Stem Cells

Adipose-derived stem cells (ADSCs) are a type of mesenchymal stem cell (MSC) with unique characteristics that make them a viable tool in RM. They possess the ability for self-renewal and can differentiate into various cell lineages, including adipocytes, chondrocytes, myocytes, osteoblasts, and neurocytes [14]. When introduced into injured areas, these cells can engage with and adapt to their environment, forming progenitor cells. Furthermore, they release growth factors, cytokines, chemokines, and micro-RNA, crucially implicated in the rejuvenation of tissue defects and normal biological function [15–18]. ADSCs are recognized as potent mediators of tissue regeneration due to their ability to secrete specific soluble factors. These ADSCs are responsible for secreting multiple growth factors, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1, hepatocyte growth factors (HGF), and transforming growth factor (TGF)-β1 [19, 20]. Further, ADSCs can differentiate into various lineages under specific culturing conditions, providing significant potential for diverse clinical applications [20].

Bone Marrow Aspirate Concentrate

Bone Marrow Aspirate Concentrate (BMAC) is a treatment that involves drawing autologous bone marrow and subjecting it to centrifugation to produce an injectate with concentrated amounts of mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), growth factors, white blood cells, and platelets. BMAC has arisen as a potential therapeutic medicine, and research demonstrates promising results and outcomes in treating chronic, degenerative musculoskeletal disease [21, 22]. It has garnered significant attention as a promising biologic tool due to its supply of pluripotent mesenchymal stem cells (MSCs) and growth factors [23, 24]. Though the mechanism of action of BMAC is not clearly understood, it offers multiple potential mechanisms by which it may offer benefits. Like adipose-derived stem cells, bone marrow–derived stem cells can differentiate into various cell types, including osteoblasts, adipocytes, chondroblasts, and neurogenic cells [24]. In cartilage regeneration, a target of RM in spine disease, bone marrow has been recognized as a source of inducible chondrogenic differentiation [25].

Growth Factors

Growth factors (GFs) are a large class of diverse molecules that can trigger and enhance a wide range of essential cellular processes, including cell differentiation, growth, proliferation, and migration [26]. Growth factors are components of the regenerative process in nearly every tissue and organ and play a crucial role in cell-to-cell communication [27]. GFs play pivotal roles during development and tissue healing, making them potentially powerful tools in RM applications. Although individual growth factors have demonstrated efficacy in some clinical settings, their use as therapeutic agents has often been restricted due to inherent limitations associated with their protein structures. They are susceptible to the local tissue environment. Specifically, growth factors possess characteristics of limited protein stability, a short half-life in circulation, rapid cell uptake, and localized tissue enzymatic inactivation. While these characteristics have evolved to ensure local tissue effect, they make the efficacy of exogenous administration difficult [27, 28].

Current Evidence for Regenerative Medicine in the Spine

Regenerative Therapies for Facet Arthropathy

Facet arthropathy is a common cause of low back pain secondary to degenerative changes. Standard practices for intervention have included facet joint injections with steroids and local anesthetic, as well as medial branch thermocoagulation or radiofrequency ablation. Multiple studies have reported positive outcomes with injecting PRP into the facet joint for pain relief and improved function in the last decade. An early case series of five patients in 2015, three of which received lumbar facet joint injections ranging from the T10–11 facet joint to the L5–S1 facet joint [29]. Two patients received facet PRP injections into the cervical facet joints. Those who underwent lumbar facet PRP treatment reported improvements in pain on a visual analogue scale (VAS) with an average follow-up time of 6–12 months. Wu et al. published two prospective trials in 2016 and 2017 [30, 31]. PRP was injected into 19 patients and 46 patients, respectively. Outcome measures included pain and function, including VAS, Oswestry disability index (ODI), and Roland Morris Disability Questionnaire (RMDQ). In the 2016 Wu et al. study, 79% of patients reported improvement in symptoms with "good" or "excellent" [30]. The 2017 study compared intra-articular PRP with intra-articular betamethasone. PRP and local anesthetic/steroids showed similar results in the short term (1 month) in terms of pain relief and function. At the 6-month follow-up, PRP showed sustained improvements in VAS, RMQ, and ODI, whereas steroids showed a return of previous levels of dysfunction and pain [31]. Additionally, a recent study in 2022 compared facet injections of PRP vs. betamethasone in 30 patients [32]. Outcomes included low back pain VAS, functional disability scores, and facet joint synovitis detected on MRI post-procedure as graded by Czervionke [33]. Both steroids and PRP improved measured clinical parameters, and MRI detected facet joint synovitis. PRP showed a greater degree of improvement in the resolution of synovitis, which may suggest a longer duration of efficacy [32]. Unfortunately, there is limited evidence for regenerative therapies for facet arthropathy.

Regenerative Therapies for Sacroiliac Joint Pain

Sacroiliac joint pain is a common cause of low back and buttock pain. Traumatic events such as falls are everyday inciting events, though spondyloarthropathies and osteoarthritis are common nontraumatic causes [34]. Patients typically can have pain with prolonged sitting, standing, or lying on the affected side. Many treatments exist, including bracing, physical therapy, medications, and procedural options. A few studies have explored the efficacy of PRP injections into the sacroiliac joint compared to steroids.

Navani et al. [35] provided one of the first case series regarding long-term follow-up of patients receiving one single injection of PRP into the sacroiliac joint after failing conservative therapy. Outcomes measured include VAS and Short Form Survey (SF-36) at 1-, 3-, 6- and 12-month intervals. All patients showed 50% or greater reduction in the VAS scale and general improvement in functional scores [35]. This study led to more extensive, randomized, controlled studies. Another study in 2017 compared 60 mg of methylprednisolone vs. PRP injections into the SI joint in 40 patients [36]. Both groups had a decrease in VAS > 50%; in the steroid group, this was not sustained at 12 weeks compared to the PRP group. The same was true for quality of life and disability scores [36].

Three recent studies used ultrasound-guided techniques to evaluate the efficacy of intra-articular SI joint PRP [37–39]. Wallace et al. [37] followed 50 patients with SI joint pain after SI joint PRP injections. Improvements in the numeric pain rating scale (NRS) were observed starting at 4 weeks and sustained at 6 months. Smaller case series of ten and four patients also showed general improvement in pain scores and disability in SI joint PRP injections performed under ultrasound guidance [38, 39]. Overall, these studies have a small number of participants, thus limiting the ability to make significant conclusions regarding the efficacy of PRP for sacroiliac joint pain.

Regenerative Therapies for Lumbar Radiculopathy

Lumbar radiculopathy occurs when a nerve root becomes compressed or irritated. Compression can be caused by a herniated disc, encroachment from adjacent facet arthropathy or spinal canal stenosis. When conservative treatment such as physical therapy and medication management fails, epidural steroid injections provided a source of pain relief for many patients. With the advent of regenerative therapies for musculoskeletal and neuropathic pain, many have proposed that epidural injections of regenerative products (PRP, BMAC) could be beneficial in reducing pain and improving function. Few studies have incorporated this practice, though initial results are promising.

Becker et al. (2007) performed epidural injections with autologous conditioned serum (ACS; Orthokine) to treat lumbar radiculopathy and compared this to two different concentrations of triamcinolone [40]. A series of 3 injections were performed in each group. All groups showed clinically significant improvement at 12 weeks in VAS and ODI, with ACS showing superiority in improvement of VAS from weeks 12 to 22 at the end of the study [40]. Similarly, another study used ACS epidural injections to treat lumbar radiculopathy and found efficacy in pain relief and improved disability scores [41]. A study of 10 patients with interlaminar epidural PRP injections showed improvements in VAS, straight leg raise test (SLRT), and Modified Oswestry Low Back Pain Disability Questionnaire (MODQ) in all patients [42]. A large trial of 470 patients utilized platelet lysate (PL) injections into the epidural space to treat radiculopathy in 470 patients [43]. Patients were followed for up to 24 months, showing improvements in NRS initially after 1 month and functional improvements up to 24 months after injections were performed [43]. They reported a complication rate of 6.3%, including post-procedural pain, skin reactions, and three patients with symptoms consistent with postdural puncture headache. All adverse events were reported to be self-limiting.

Regenerative Therapies for Discogenic Pain

Pain of discogenic origin presents as lumbar discomfort without concurrent radicular symptoms. Symptoms can be present at rest and with activity. While many clinical factors are considered while diagnosing discogenic pain, MRI assessment reveals Type I Modic changes, annular tears, disc desiccation, and many other findings that help pinpoint anatomic targets for intervention [44]. Provocative discography can also be considered a diagnostic tool. Given the anti-inflammatory properties of PRP and BMAC, these therapies have also been utilized to improve pain and function.

Many studies included patients who have failed conservative therapy with > 6 months of low back pain and concordant pain on discography. A study of 47 patients (29 treatment, 18 control group) evaluated the efficacy of lumbar intradiscal PRP [45]. The PRP group had improvements in functional scores, NRS, and satisfaction scores over the first 8 weeks. Functional score improvements continued through the 12-month survey [45]. Levi et al. [46] collected data on 22 patients by injecting PRP at primarily 1–2 disc levels in the lumbar spine and followed up patients over 6 months. Primary endpoints included categorical success defined as > 50% VAS improvement and > 30% ODI improvement. A total of 47% of patients met categorical success defined by the authors at the 6-month follow-up [46]. Akeda et al. (2017) evaluated intradiscal PRP in the lumbar spine, which showed a decreased mean VAS score on average 4.0 points on a 10-point scale at 48 weeks of follow-up [47]. Navani et al. (2018) studied PRP and BMAC in patients with chronic discogenic pain [48]. PRP was used for mildly degenerated discs (Pfirman index 1–2), while BMAC was used for more severely degenerated discs (Pfirman index 3–4). At 18 months, 93% (14/15) of patients reported greater than 50% relief and increased function. Medication use also decreased in 80% of patients at 18 months [48]. Conversely, a recent RCT in 2022 with 26 patients (8 saline and 18 intradiscal PRP) found no clinically significant pain relief, defined as a 30% reduction in NPRS and ODI, in patients in either the PRP or saline group [49•]. Additionally, a comparative evaluation of intradiscal radiofrequency ablation and PRP for discogenic low back pain with 24 patients in each group found no statistically significant difference in NRS and ODI between the groups at 6 months. However, within each group, the NRS and ODI decreased significantly at 6 months [50].

Other smaller studies have investigated intradiscal BMAC to improve pain and function. Sample sizes ranged from 10 to 26 patients, only one study was controlled, and measurements included pain scores, functional scores, and quality-of-life surveys. The average follow-up was 12 months. Most studies showed improvement in pain and function up to 12 months of varying degrees, though more extensive randomized controlled studies are required to make further conclusions [51–57].

Discussion

Each RM therapeutic approach discussed in this review reveals a multifaceted mechanism of action not observed in more traditional therapies. Each application shows a more complete healing profile by affecting numerous growth factors involved in key biochemical pathways associated with angiogenesis, tissue growth, and inflammation. This would, preliminary at least, position RM as a meaningful next step in managing spine-related pain after conservative therapy has failed. Early results show some promise with minimal risk of adverse event. A 2022 systematic review including 12 studies

and 1092 patients who received epidural injections with PRP showed a low incidence of common adverse effects, including post-procedural inflammation, soreness, muscle tightening, stiffness, numbness, and post-dural puncture headaches [58•]. Among the pooled patients, the incidence rate was similar to that of previously reported epidural steroid injections, including no reported severe complications particular to epidural injections, such as arachnoiditis, neuraxial hematoma, infection, nerve injury, or spinal cord infarct. While no events occurred in this pooled population, the sample size remains too small for meaningful conclusions.

As it stands, evidence supporting the use of RM remains weak. In 2019, a meta-analysis showed marginal effectiveness of PRP in orthopedic procedures for the following disorders: plantar fasciitis, Achilles tendinopathy, patellar tendinopathy, rotator cuff tendinopathy, and lateral epicondylitis [59]. The authors evaluated 36 randomized controlled trials across 2073 patients. The studies evaluated in this review evaluated small patient populations with a limited long-term follow-up. Studies also lack consistency regarding inclusion and exclusion criteria, method of preparation, and proceduralist technique [60, 61]. Furthermore, study designs and measured outcomes varied; only some studies had follow-up visits beyond 12 months. Additionally, there are the economic constraints associated with RM. PRP and BMAC injections have a substantial upfront cost to the patient, and therefore, long-term outcomes are required to determine the cost-to-benefit ratio. Given the variability of published studies, it is difficult to make conclusions regarding the efficacy of PRP, MSCs, ADSCs, BMAC, and growth factors for spine-related pathologies. Further randomized controlled trials with standardized protocols and long-term outcomes are necessary. There must also be consensus concerning the method of preparation and treatment protocol. Finally, while the literature surrounding RM therapies is growing, continued research on effectiveness at varied injection sites such as epidural, facet joint, sacroiliac, and intradiscal is needed.

Conclusion

In conclusion, RM therapies, including PRP, MSCs, ADSCs, BMAC, and growth factors, lack the evidence required to make recommendations for the treatment of chronic spinal conditions. Although several studies demonstrate a comprehensive mechanism of action and decrease in patient pain, there is not enough evidence to justify RM's transition from bench to bedside, currently. The promise of RM as a safe and effective therapeutic approach remains real and remains encouraged about RM's progress and confident it will become a viable therapy in the future.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Sharma P, Kumar A, Dey AD. Cellular therapeutics for chronic wound healing: future for regenerative medicine. Curr Drug Targets. 2022;23:1489–504.
2. Chen H, Zhang A, Wu JC. Harnessing cell pluripotency for cardiovascular regenerative medicine. Nat Biomed Eng. 2018;2:392–8.
3. Mansouri V, Beheshtizadeh N, Gharibshahian M, Sabouri L, Varzandeh M, Rezaei N. Recent advances in regenerative medicine strategies for cancer treatment. Biomed Pharmacother. 2021;141:111875.
4. Suman S, Domingues A, Ratajczak J, Ratajczak MZ. Potential clinical applications of stem cells in regenerative medicine. Adv Exp Med Biol. 2019;1201:1–22.
5. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010;24:769–81.
6. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478–91.
7. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. Int J Mol Sci. 2020;21.
8. Ramaswamy Reddy SH, Reddy R, Babu NC, Ashok GN. Stem-cell therapy and platelet-rich plasma in regenerative medicines: a review on pros and cons of the technologies. J Oral Maxillofac Pathol. 2018;22:367–74.
9. Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets. 2013;24:173–82.
10. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent. 2001;10:225–8.
11. Everts PA, Knape JT, Weibrich G, Schonberger JP, Hoffmann J, Overdevest EP, et al. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol. 2006;38:174–87.
12. Sheth U, Simunovic N, Klein G, Fu F, Einhorn TA, Schemitsch E, et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: a meta-analysis. J Bone Joint Surg Am. 2012;94:298–307.
13. Tomoyasu A, Higashio K, Kanomata K, Goto M, Kodaira K, Serizawa H, et al. Platelet-rich plasma stimulates osteoblastic differentiation in the presence of BMPs. Biochem Biophys Res Commun. 2007;361:62–7.

14. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145–7.
15. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. Circ Res. 2007;100:1249–60.
16. Nakagami H, Maeda K, Morishita R, Iguchi S, Nishikawa T, Takami Y, et al. Novel autologous cell therapy in ischemic limb disease through growth factor secretion by cultured adipose tissue-derived stromal cells. Arterioscler Thromb Vasc Biol. 2005;25:2542–7.
17. Rehman J, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation. 2004;109:1292–8.
18. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, et al. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell. 2008;2:141–50.
19. Tsuji W, Rubin JP, Marra KG. Adipose-derived stem cells: implications in tissue regeneration. World J Stem Cells. 2014;6:312–21.
20. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13:4279–95.
21. Cotter EJ, Wang KC, Yanke AB, Chubinskaya S. Bone marrow aspirate concentrate for cartilage defects of the knee: from bench to bedside evidence. Cartilage. 2018;9:161–70.
22. Chahla J, Mannava S, Cinque ME, Geeslin AG, Codina D, LaPrade RF. Bone marrow aspirate concentrate harvesting and processing technique. Arthrosc Tech. 2017;6:e441-e4e5.
23. Indrawattana N, Chen G, Tadokoro M, Shann LH, Ohgushi H, Tateishi T, et al. Growth factor combination for chondrogenic induction from human mesenchymal stem cell. Biochem Biophys Res Commun. 2004;320:914–9.
24. Kim GB, Seo MS, Park WT, Lee GW. Bone marrow aspirate concentrate: its uses in osteoarthritis. Int J Mol Sci. 2020;21.
25. Johnstone B, Hering TM, Caplan AI, Goldberg VM, Yoo JU. In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. Exp Cell Res. 1998;238:265–72.
26. Ren X, Zhao M, Lash B, Martino MM, Julier Z. Growth factor engineering strategies for regenerative medicine applications. Front Bioeng Biotechnol. 2019;7:469.
27. Mitchell AC, Briquez PS, Hubbell JA, Cochran JR. Engineering growth factors for regenerative medicine applications. Acta Biomater. 2016;30:1–12.
28. Lee K, Silva EA, Mooney DJ. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. J R Soc Interface. 2011;8:153–70.
29. Aufiero D, Vincent H, Sampson S, Bodor M. Regenerative injection treatment in the spine: review and case series with platelet rich plasma. J Stem Cells Res Rev & Rep. 2015;2(1):1019.
30. Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, 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;19:617–25.
31. Wu J, Zhou J, Liu C, Zhang J, Xiong W, Lv Y, et al. A prospective study comparing platelet-rich plasma and local anesthetic (LA)/corticosteroid in intra-articular injection for the treatment of lumbar facet joint syndrome. Pain Pract. 2017;17:914–24.
32. Kotb SY, Sherif NM, Saleh HA, Ahmed SF, Sakr HM, Taeimah MO. The role of intra-articular injection of autologous platelet-rich plasma versus corticosteroids in the treatment of synovitis in lumbar facet joint disease. Saudi Med J. 2022;43:1200–8.
33. Czervionke LF, Fenton DS. Fat-saturated MR imaging in the detection of inflammatory facet arthropathy (facet synovitis) in the lumbar spine. Pain Med. 2008;9:400–6.
34. Raj MA, Ampat G, Varacallo M. Sacroiliac joint pain. Treasure Island, FL: StatPearls Publishing; 2023.
35. Navani A, Gupta D. Role of intra-articular platelet-rich plasma in sacroiliac joint pain. Tech Reg Anesth Pain Manag. 2015;19:54–9.
36. Singla V, Batra YK, Bharti N, Goni VG, Marwaha N. Steroid vs. platelet-rich plasma in ultrasound-guided sacroiliac joint injection for chronic low back pain. Pain Pract. 2017;17:782–91.
37. Wallace P, Bezjian Wallace L, Tamura S, Prochnio K, Morgan K, Hemler D. Effectiveness of ultrasound-guided platelet-rich plasma injections in relieving sacroiliac joint dysfunction. Am J Phys Med Rehabil. 2020;99:689–93.
38. Ko GD, Mindra S, Lawson GE, Whitmore S, Arseneau L. Case series of ultrasound-guided platelet-rich plasma injections for sacroiliac joint dysfunction. J Back Musculoskelet Rehabil. 2017;30:363–70.
39. de Sire A, Lippi L, Mezian K, Calafiore D, Pellegrino R, Mascaro G, et al. Ultrasound-guided platelet-rich-plasma injections for reducing sacroiliac joint pain: a paradigmatic case report and literature review. J Back Musculoskelet Rehabil. 2022;35:977–82.
40. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Kramer J, Willburger RE. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression: an investigator-initiated, prospective, double-blind, reference-controlled study. Spine (Phila Pa 1976). 2007;(32):1803–8.
41. Ravi Kumar HS, Vijay GG, Batra YK. Autologous conditioned serum as a novel alternative option in the treatment of unilateral lumbar radiculopathy: a prospective study. Asian Spine J. 2015;9:916–22.
42. Bhatia R, Chopra G. Efficacy of platelet rich plasma via lumbar epidural route in chronic prolapsed intervertebral disc patients-a pilot study. J Clin Diagn Res. 2016;10:UC05-UUC7.
43. 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;4:38.
44. Fujii K, Yamazaki M, Kang JD, Risbud MV, Cho SK, Qureshi SA, et al. Discogenic back pain: literature review of definition, diagnosis, and treatment. JBMR Plus. 2019;3:e10180.
45. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: a prospective, double-blind, randomized controlled study. PM R. 2016;8:1–10 quiz.
46. Levi D, Horn S, Tyszko S, Levin J, Hecht-Leavitt C, Walko E. Intradiscal platelet-rich plasma injection for chronic discogenic low back pain: preliminary results from a prospective trial. Pain Med. 2016;17:1010–22.
47. Akeda K, Ohishi K, Masuda K, Bae WC, Takegami N, Yamada J, et al. Intradiscal injection of autologous platelet-rich plasma releasate to treat discogenic low back pain: a preliminary clinical trial. Asian Spine J. 2017;11:380–9.
48. Navani A, Ambach MA, Navani R, Wei J. Biologics for lumbar discogenic pain: 18-month follow-up for safety and efficacy. Interv Pain Manag Rep (Case Report). 2018;2:111–8.
49.• Zielinski MA, Evans NE, Bae H, Kamrava E, Calodney A, Remley K, et al. Safety and efficacy of platelet rich plasma for treatment of lumbar discogenic pain: a prospective, multicenter, randomized, double-blind study. Pain Physician. 2022;25:29–34.**This is one of the few prespective, randomized, double-blind study evaluating platelet-rich plasma for discogenic back pain.**
50. Goyal T, Paswan AK, Jain D, Verma N, Dubey RK. Comparative evaluation of efficacy of percutaneous intradiscal radiofrequency ablation and platelet rich plasma injection for discogenic low back pain: a prospective randomized trial. J Musculoskelet Res. 2022;25.
51. Noriega DC, Ardura F, Hernandez-Ramajo R, Martin-Ferrero MA, Sanchez-Lite I, Toribio B, et al. Intervertebral disc repair

by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. Transplantation. 2017;101:1945–51.
52. Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up. Int Orthop. 2017;41:2097–103.
53. Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. Int Orthop. 2016;40:135–40.
54. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. Stem Cells. 2015;33:146–56.
55. Coric D, Pettine K, Sumich A, Boltes MO. Prospective study of disc repair with allogeneic chondrocytes presented at the 2012 Joint Spine Section Meeting. J Neurosurg Spine. 2013;18:85–95.
56. Orozco L, Soler R, Morera C, Alberca M, Sanchez A, Garcia-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. Transplantation. 2011;92:822–8.
57. Kumar H, Ha DH, Lee EJ, Park JH, Shim JH, Ahn TK, et al. Safety and tolerability of intradiscal implantation of combined autologous adipose-derived mesenchymal stem cells and hyaluronic acid in patients with chronic discogenic low back pain: 1-year follow-up of a phase I study. Stem Cell Res Ther. 2017;8:262.
58.• Kubrova E, Martinez Alvarez GA, Her YF, Pagan-Rosado R, Qu W, D'Souza RS. Platelet rich plasma and platelet-related products in the treatment of radiculopathy-a systematic review of the literature. Biomedicines. 2022;10. **This is a great systematic review of current literature for PRP and the safety profile of PRP.**
59. Franchini M, Cruciani M, Mengoli C, Marano G, Pupella S, Veropalumbo E, et al. Efficacy of platelet-rich plasma as conservative treatment in orthopaedics: a systematic review and meta-analysis. Blood Transfus. 2018;16:502–13.
60. Ruiz-Lopez R, Tsai YC. A randomized double-blind controlled pilot study comparing leucocyte-rich platelet-rich plasma and corticosteroid in caudal epidural injection for complex chronic degenerative spinal pain. Pain Pract. 2020;20:639–46.
61. Lana JFSD, da Fonseca LF, Macedo RDR, Mosaner T, Murrell W, Kumar A, et al. Platelet-rich plasma vs bone marrow aspirate concentrate: an overview of mechanisms of action and orthobiologic synergistic effects. World J Stem Cells. 2021;13:155–67.

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