Regenerative Medicine

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Introduction

Regenerative medicine encompasses approaches to treat pain by using mostly biologic compounds with the goal of repairing damaged tissues. This chapter will address two main implements of this branch of pain medicine: platelet-rich plasma (PRP) and stem cells.

Platelet-Rich Plasma (PRP)

History

The concept of regenerative medicine existed long before stem cells or platelet-rich plasma (PRP). In Aristotle's time, observations of salamander tail regeneration started to inform the concepts of the body's regenerative capacity. PRP was used as early as the 1950s for dermatologic conditions [1]. In 1987, PRP was used during open-heart surgery to augment healing and to avoid homologous blood product transfusion [2]. In the 1990s, PRP use gradually increased, especially in oral maxillofacial surgery, where it was associated with improved graft success [3]. In the 2000s, PRP grew in popularity in the fields of orthopedics and sports medicine, given its promise of augmenting the body's natural bone-healing mechanisms [4]. Mishra and Pavelko in 2006 integrated PRP into the specialty of pain management by showing a significant reduction in pain after PRP injection for chronic lateral epicondylitis [5]. The use of PRP by athletes such as Hines Ward and Tiger Woods has accelerated the interest in PRP for musculoskeletal conditions in both the medical and public world.

Definition

Platelet-rich plasma (PRP) is defined as plasma with supraphysiologic concentrations of platelets and other cellular components. The normal range for platelets in whole blood is 150,000–450,000 platelets per microliter. While there is no standardized concentration of platelets and other cell types that is required for PRP, in general the range is between 3 and 9× baseline concentration. Greater than four times baseline platelet concentration or 1–1.5 million/microL of platelets is thought to be therapeutic [6–8]. Additionally, there are no standardized mechanisms for collecting and preparing PRP. As a result, there are qualitative and quantitative differences between injectates, making research and evaluation of efficacy extremely difficult.

Platelets contain a plethora of growth factors, enzymes, and other bioactive compounds within alpha-granules that are involved in wound and tissue healing [1]. The main growth factors associated with tissue healing are platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-B), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), hepatocyte growth factor (HGH), fibroblast growth factor (FGF), and epidermal growth factor (EGF) [9]. Appropriate concentrations and presence of white blood cells (WBC) are currently under debate. The concern regarding WBC and neutrophils is that their activating role in the inflammatory process could further exacerbate and delay healing [10, 11].

Currently, there are a variety of PRP classification systems. The revised system formed by Dohan Ehrenfest consists of four groups: pure platelet-rich plasma (P-PRP),

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Table 36.1 PLRA Classification

PLRA classification		Criteria	Final score
P	Platelet count	Volume injected	Cells/μL
L	Leukocyte content	>1%	+
		<1%	–
R	Red blood cell content	>1%	+
		<1%	–
A	Activation	Yes	+
		No	–

leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte- and platelet-rich fibrin (L-PRF) [12]. Another sports medicine-centered classification system focuses on the concentration of platelets and leukocytes and whether the sample is activated. There are four groups: L-PRP solution, L-PRP gel, P-PRP solution, and P-PRP gel [13]. The PLRA classification system (Table 36.1) proposed by Mautner attempts to include the critical components from the other classification systems: platelet concentration, leukocyte concentration, red blood cells, activation agent, and volume of injectate. The PLRA system's goal is to standardize the important aspects of the injectate in order to make evaluation of treatment outcomes more meaningful [14].

Derivation

PRP is derived from a sample of autologous whole blood drawn from the patient. Sterile precautions are extremely important when collecting the patient's blood in order to prevent infection [4]. Additionally, care should be used to avoid unnecessary trauma to prevent premature activation of platelets and the clotting cascade. Currently, there are a variety of different systems and processes used for PRP preparation. These vary in initial volume of the whole blood, final volume, final concentration of leukocytes, platelets, and other growth factors, rate and number of cycles, spin time of centrifuge, and the addition of an activating agent. In general, once the blood is drawn, an anticoagulant (citrate-dextrose) is added to prevent activation of the clotting cascade. The sample is then prepared using one of two general methods: PRP or buffy-coat. In the PRP method, two cycles of centrifugation are performed: the first cycle, termed the soft spin (1200–1500 RPM), separates the RBCs from the remaining whole blood and the second cycle, termed the hard spin (4000–7000), separates PRP from the platelet-poor plasma (PPP). In the buffy-coat method, high-speed centrifugation is performed, separating the sample into three layers: red blood cells, buffy-coat (platelets/white blood cells), and PPP [15]. The buffy-coat layer is then centrifuged again resulting in a higher concentration of platelets.

Indications/Uses

Tendon Pathology

Overuse injuries are common and can affect tendons throughout the body, and ultimately lead to tendinosis. In general, tendon healing is slower than other tissues due to poor vascular supply. PRP has been used to treat a variety of different tendon pathologies. Some of the best data for PRP use is in the treatment of lateral epicondylitis, also known as tennis elbow. The incidence of lateral epicondylitis can be as high as 2% [16]. Mishra and Pavelko first illustrated the promise of PRP in their sentinel unblinded study of 20 patients with lateral epicondylitis. They showed significant improvement in VAS scores following PRP injection at up to 3 years post-injection [5]. In a randomized double-blinded controlled trial of 100 patients comparing steroid and PRP injections for lateral epicondylitis, there was significant improvement in both VAS and DASH scores at 26 and 52 weeks in the PRP group [17]. Additionally, at 2-year follow-up, 81% of the PRP group had >25% reduction in their VAS scores compared to only 40% of those in the steroid group [17]. Conversely, in a randomized double-blinded study comparing steroid, saline, and PRP injection for lateral epicondylitis, there was no statistical difference between the groups [18].

PRP has also been shown to be an effective treatment for other tendinopathies such as plantar fasciitis and Achilles tendinosis [19]. Jain and colleagues in a randomized trial of 60 patients comparing PRP and steroid injections for plantar fasciitis demonstrated a significant improvement in VAS, range of motion, and American Orthopaedic Foot and Ankle Surgery (AOFAS) scores at 1 year [20]. Of note, there was no statistical difference at either 3 or 6 months. In a randomized study of 40 patients comparing steroids to PRP injections for chronic plantar fasciitis, PRP was shown to be more effective, with improved AOFAS scores at 3, 6, 12, and 24 months [21].

Intra-articular Pathology

As with tendinous pathologies, intra-articular cartilage injuries and degeneration exhibit slow and poor healing. Knee osteoarthritis (OA) is extremely common and has a tremendous economic burden on our society. As of 2012, approximately 46 million Americans suffer from knee OA, with nearly 50% of people over the age of 85 having symptomatic knee OA [22]. OA is thought to be secondary to an imbalance of pro-inflammatory and anti-inflammatory cytokines ultimately leading to cartilage destruction [23]. PRP has been shown to not only mediate the inflammatory response and improve vascular supply but also to stimulate chondrogenesis [24]. In a large meta-analysis and systemic

review of PRP for knee OA, PRP injections demonstrated efficacy at 6–12 months [25, 26]. Additionally, there was a trend toward superiority over viscosupplementation in both duration of action and reduction in pain [25]. Interestingly, the reduction in pain scores was significantly greater in patients with mild to moderate OA compared to more severe cases [26]. Conversely, in a large randomized controlled trial of 443 patients, PRP was shown to be no more effective than viscosupplementation [27]. Of note, both interventions showed improvement in pain scores and functionality. PRP injections have been used to treat arthritis in other joints. A randomized controlled trial comparing PRP alone to PRP and hyaluronic acid (HA) and HA alone for hip OA revealed that the PRP group had lower VAS scores at 2, 6, and 12 months post-injection, but the results were only clinically significant at 6 months [28].

Ligament Pathology

Current randomized trials are limited for PRP use for ligament injuries, although interest of using PRP for partial tears as an alternative to surgery is increasing. Avoiding surgery while expediting and optimizing healing is of extreme interest especially in the world of athletics. In a retrospective study of 44 pitchers receiving one to three PRP injection following partial ulnar collateral ligament tears, the patients had significantly better outcomes compared to prior conservative therapy standards [29, 30]. Using the modified Conway scale, 15 patients had excellent results, 17 had good results, 2 had fair results, and 10 had poor outcomes. Of note, 4 out of 6 of the professional pitchers in the study were able to return to pitch in Major League Baseball. PRP has also been used to improve healing following anterior cruciate ligament (ACL) injuries. A large systematic review did not show any clinically significant benefit of using PRP during ACL repair surgery [31].

Disc and Spine Pathology

Presently, there is growing interest in the application of PRP to the treatment of low back pain, although current research is still limited. Facet joints are synovial joints, and like peripheral synovial joints may develop degenerative changes secondary to injury or overuse. As a result, the use of PRP may be an effective treatment to both decrease inflammation and stimulate healing. In a small prospective study, 19 patients with facet joint syndrome received intra-articular facet joint injections with PRP [32]. Patients were followed up for 3 months, and 15 of the 19 patients had either good or excellent relief [32]. These results are encouraging, but this study is significantly limited secondary to the absence of a control group.

PRP is also being explored as a treatment option for symptomatic degenerative disc disease. A recent double-blind randomized controlled study demonstrated significant improvement at 8 weeks in the Numeric Rating Scale (NRS), Functional Rating Index (FRI), and North American Spine Society (NASS) Outcome Questionnaire compared to the control group after patients received an intradiscal PRP injection [33]. Additionally, patients in the treatment group maintained significant improvement in their FRI score at 1 year [33].

PRP has also been used to treat sacroiliac (SI) joint pain. In a small case series of four patients with SI joint instability and chronic severe back pain, PRP was injected into the SI joint and patients were followed up at 12 and 48 months [34]. At 12 months, all patients reported significant improvement in their joint stability, back pain, and quality of life. These results were maintained at 48 months.

Complications and Contraindications

In general, if the sample is prepared appropriately using sterile technique and the procedure is performed with image guidance, the risk of complications is limited. As with any injection, there is a risk of bleeding or infection. Additionally, surrounding structures such nerves and vasculature can be injured. Although it is common to have an initial increase in pain following the injection, persistent worsening of pain is also possible [17]. Of note, for the initial increase in a pain following the procedure, it is preferred to avoid NSAIDs secondary to their inhibitory effects on platelets. There are a variety of absolute and relative contraindications to PRP injection, including but not limited to thrombocytopenia, platelet dysfunction, infection (systemic or local), anticoagulant therapy, metastatic cancer, and pregnancy.

Future Directions

The future of PRP for musculoskeletal pathology is promising. PRP injections are minimally invasive and have an excellent safety profile, making PRP a desirable treatment option. Currently, PRP research lacks standardization and in order to truly elucidate and demonstrate its effects, we will need to develop more consistent research models. Presently, the exact composition of different cell types and growth factors needed to optimize tissue healing is unknown.

Stem Cells

Terminology

Stem cells refer to lines of cells capable of proliferating and subsequently differentiating into the many tissues of an organism. This has sparked much ethical debate especially since the capability of harvesting them from human embryos became a reality in 1998. Given that disease processes that result in chronic pain are often result from an inability to regenerate damaged tissue, stem cell research has the potential to revolutionize the management of many chronic pain syndromes such as osteoarthritis, neuropathies, and tendinopathies [35]. Prior to reviewing this complex topic, key definitions are listed in Table 36.2.

Derivation and Techniques

Embryonic stem cells (ES) are collected from preimplantation blastocysts. In the past, stem cells were removed from embryos fertilized in vitro or created from somatic cell nuclear transfer. Somatic cell nuclear transfer (SCNT) is the process of cloning in which a nuclear material from a somatic cell is transplanted into an enucleated egg cell. This ultimately produces an embryo genetically identical to the somatic donor. Embryos were allowed to form an inner cell mass which was abundant in stem cells. Harvesting the cells at this level of development led to the destruction of the embryo. Consequently, this process was the center of much of the ethical debate surrounding embryonic stem cell research. A newer process called altered nuclear transfer (ANT) proceeds much in the same manner as SCNT; however, the nuclear contents are modified to prevent the formation of a human embryo and still produce stem cells. Another new technique called blastomere extraction removed one of the eight blastomeres formed from a 2-day-old embryo, in which the remaining seven blastomeres were capable of being re-implanted into the mother and subsequently allowed to develop into healthy human embryos, assuming no defects were detected in genetic testing.

Table 36.2 Key Definitions

Type of cells	Definition
Stem	Cells capable of self-renewal and differentiation
Totipotent	Capacity to differentiate into embryonic and extra-embryonic tissues (placental)
Pluripotent	Capacity to differentiate into tissue of the body derived from the embryonic germ layers that form the inner mass in the blastocyst (endoderm, mesoderm, ectoderm)
Multipotent	Capacity to differentiate into any cells of a particular germ layer
Unipotent	Capacity to differentiate into only one cell type

Adult stem cells (AS) are present in most tissues to maintain tissue and repair injuries. Hematopoietic stem cells differentiate into the various blood cell lines and are collected from bone marrow and peripheral blood. Bone marrow and blood is typically extracted from the hip using a large specialized needle. The aspirate undergoes a process called apheresis using a special machine in which stem cells were separated out from bone fragments, fat, and other components. Peripheral blood can also be used to obtain hematopoietic stem cells, although they are much fewer in number than in the bone marrow. Much of the interest in stem cells relating to pain management involves mesenchymal cells (MSCs) which give rise to fat, bone, cartilage, and connective tissue. Though they have classically been isolated from bone marrow, new techniques allow them to be obtained from fat using a less invasive liposuction procedure. The removed tissue then undergoes further filtration processes to isolate MSCs. The cells can then be grown in standard culture with different media, matrixes, cytokines, and growth factors to achieve desired differentiation.

Induced pluripotent stem cells (IPS) are obtained by a process of introducing genes present in pluripotent stem cells into mature cells when those genes are not typically expressed. This results in a few of those cells reverting back to a more immature, less differentiated state [36].

Therapeutic Targets

Discogenic Pain

The treatment of chronic lower back pain has been one of the most common uses of human mesenchymal stem cells in pain management. The process entails integration of cultured MSCs derived from bone marrow with nucleus pulposus cells to stimulate chondrogenic differentiation. These cells are then injected into degenerative discs in which they would serve to regenerate and buttress collagen matrices. Multiple small nonrandomized, uncontrolled studies have reported improvement in pain scores during a 1–2-year follow-up. One study following 10 patients with injection of BMSCs into the annulus fibrosis showed improvement in pain scores for low back and radicular pain [37].

The largest randomized controlled trial was initiated in 2007 in which 28 canine subjects were randomized to have percutaneous injection of damaged disc-derived chondrocytes injected into the annulus fibrosis 12 weeks after microdiscectomy or have microdiscectomy alone. MRI was used to confirm decreased reduction in disc height in the experimental group, with decreased pain scores, and decreased disability. It was also found that the experimental group had evidence of new proteoglycan and collagen formation in degenerative

areas the level of injection [38]. Other studies have shown that injection of stem cells within intervertebral discs result in no improvement in lower back pain [39]. There is no consensus on this novel use of MSCs, though many studies are encouraging. Larger blinded RTCs are needed to further investigate intradiscal stem cell therapy to help elucidate its utility.

Osteoarthritis

There are no current FDA treatments approved for the use of stem cell injections to repair or regenerate damaged cartilage in osteoarthritis; however, research is ongoing. Mechanisms behind improvement in cartilage have been hypothesized to be due to secretion and promotion of growth factors/cytokines to repair damaged tissue and inhibition of MMP-13, a protein produced by chondrocytes that damages cartilage in OA. Several research projects are attempting to discern the efficacy of cartilage repair using injected autologous chondrocytes in comparison to mesenchymal stem cells. Most researchers speculate that MSCs should provide significant advantages over autologous chondrocytes due to abundance in all tissues, improved responsiveness to biologic and artificial manipulation, broad range of expression, and capacity to differentiate into regenerative tissue [40]. Studies have demonstrated that although the capacity to differentiate does not change with age, shear cell number and proliferative potential do decline. A small cohort study showed marked improvement in pain scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) after intra-articular injection of MSCs in a total of 12 patients who previously failed conservative management. T2 MRI showed improvement in knee cartilage quality and no adverse outcomes were reported [41]. Another randomized trial compared intra-articular knee injections of hyaluronic acid and MSCs and found that both groups reported improved pain, but cartilage quality appeared superior in the stem cell group [42]. Numerous other studies have been undertaken concluding that stem cell injections into joints have contributed to the healing of native cartilage [43]. Joint injection procedures have had a low incidence of adverse events, but do include pulmonary embolism, tumor formation, and joint infection [44]. Mechanisms behind improved cartilage profiles have been hypothesized to be due to secretion and promotion of growth factors/cytokines to repair damaged tissue and inhibition of MMP-13, a protein produced by chondrocytes that damages cartilage in OA [45]. Many more clinical trials need to be undertaken with greater number of patients to make a more definitive statement regarding likely benefits of intra-articular stem cell injections in the treatment of OA.

Neuropathic Pain

Target diseases of most neuropathic pain studies involving stem cells include trigeminal neuralgia and diabetic neuropathy. Various mechanisms have been theorized including immunomodulation resulting in decreased inflammatory response to injured tissue, angiogenic stimulation resulting in improved vascularity and oxygen delivery to affected sites. A study using spinal cord injury in a rat model showed that neuropathic pain may be reduced with transplantation of BM-MSCs or UC-MSCs, but motor function recovery, hyperalgesia, and allodynia appear to be unchanged [46]. A recent study with eight patients with trigeminal neuralgia that failed pharmacotherapy showed that majority of patients reported improved pain and decreased gabapentin requirements after intraneural injections of adipose MSCs. In another small study, 10 out of 15 patients reported improvement in pudendal neuropathy after injection [47]. Studies on stem cells targeting diabetic neuropathy have not yet been conducted in human model, although animal studies have shown promise [48].

Tendinopathies

Tendon injury remains a common cause of discomfort, pain, and limitation in population typically stemming from inflammation and overuse injury. Stem cells are currently being researched to aid in tendon repair due to their capacity to differentiate into tenocytes, perform proliferative and synthetic function, and secrete growth factors to aid in regeneration of tendon tissue. MSCs are preferred over ECs and iPSCs for their decreased likelihood of teratoma formation given their restricted self-renewal and lineage differentiation potential. BMSCs do still have the potential to form ectopic bone in transplant injection sites. Pretreatment of MSCs with specific growth factors to drive tenogenic differentiation prior to treatment has largely shown success in improved healing. Delivery of stem cells via intralesional injection or direct transplantation has shown the greatest likelihood of stem cells taking residence in target tissue. Two studies assessing the injection of allogeneic ADSCs cells for treatment of chronic lateral epicondylitis have yielded positive results [49]. As stated previously, the majority of these studies are in animal models and have short follow-up periods of 4–12 weeks. Most studies in human are small and uncontrolled, and as such, there is no FDA-approved stem cell treatment of tendinopathies in humans at this time.

References

1. Sprugel KH, McPherson JM, Clowes AW, Ross R. Effects of growth factors in vivo. I. Cell ingrowth into porous subcutaneous chambers. Am J Pathol. 1987;129(3):601–13.
2. Ferrari M, Zia S, Valbonesi M, Henriquet F, Venere G, Spagnolo S, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery. Int J Artif Organs. 1987;10(1):47–50.
3. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(6):638–46.
4. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg. 2009;17(10):602–8.
5. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am J Sports Med. 2006;34(11):1774–8.
6. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62(4):489–96.
7. Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: a review and author's perspective. J Cutan Aesthet Surg. 2014;7(4):189–97.
8. Giusti I, Rughetti A, D'Ascenzo S, Millimaggi D, Pavan A, Dell'Orso L, et al. Identification of an optimal concentration of platelet gel for promoting angiogenesis in human endothelial cells. Transfusion. 2009;49(4):771–8.
9. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91(1):4–15.
10. Scott A, Khan KM, Roberts CR, Cook JL, Duronio V. What do we mean by the term "inflammation"? A contemporary basic science update for sports medicine. Br J Sports Med. 2004;38(3):372–80.
11. Tidball JG. Inflammatory processes in muscle injury and repair. Am J Physiol Regul Integr Comp Physiol. 2005;288(2):R345–53.
12. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J. 2014;4(1):3–9.
13. Mishra A, Harmon K, Woodall J, Vieira A. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol. 2012;13(7):1185–95.
14. Mautner K, Malanga GA, Smith J, Shiple B, Ibrahim V, Sampson S, et al. A call for a standard classification system for future biologic research: the rationale for new PRP nomenclature. PM R. 2015;7(4 Suppl):S53–9.
15. Fitzpatrick J, Bulsara MK, McCrory PR, Richardson MD, Zheng MH. Analysis of platelet-rich plasma extraction: variations in platelet and blood components between 4 common commercial kits. Orthop J Sports Med. 2017;5(1):2325967116675272.
16. Verhaar JA. Tennis elbow. Anatomical, epidemiological and therapeutic aspects. Int Orthop. 1994;18(5):263–7.
17. 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(2):255–62.
18. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med. 2013;41(3):625–35.
19. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. Foot Ankle Int. 2012;33(5):379–85.
20. Jain K, Murphy PN, Clough TM. Platelet rich plasma versus corticosteroid injection for plantar fasciitis: a comparative study. Foot. 2015;25(4):235–7.
21. Monto RR. Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis. Foot Ankle Int. 2014;35(4):313–8.
22. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. Pain Med. 2012;13(6):740–53.
23. Goldring MB. The role of the chondrocyte in osteoarthritis. Arthritis Rheum. 2000;43(9):1916–26.
24. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med. 2008;1(3–4):165–74.
25. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy. 2013;29(12):2037–48.
26. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2014;95(3):562–75.
27. Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. Am J Sports Med. 2015;43(7):1575–82.
28. Dallari D, Stagni C, Rani N, Sabbioni G, Pelotti P, Torricelli P, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. 2016;44(3):664–71.
29. Dines JS, Williams PN, ElAttrache N, Conte S, Tomczyk T, Osbahr DC, et al. Platelet-rich plasma can be used to successfully treat elbow ulnar collateral ligament insufficiency in high-level throwers. Am J Orthop. 2016;45(5):296–300.
30. Rettig AC, Sherrill C, Snead DS, Mendler JC, Mieling P. Nonoperative treatment of ulnar collateral ligament injuries in throwing athletes. Am J Sports Med. 2001;29(1):15–7.
31. Figueroa D, Figueroa F, Calvo R, Vaisman A, Ahumada X, Arellano S. Platelet-rich plasma use in anterior cruciate ligament surgery: systematic review of the literature. Arthroscopy. 2015;31(5):981–8.
32. 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(8):617–25.
33. 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):1–10; quiz
34. 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(2):363–70.
35. Chakravarthy K, Chen Y, He C, Christo PJ. Stem cell therapy for chronic pain management: review of uses, advances, and adverse effects. Pain Physician. 2017;20(4):293–305.
36. Hospital BCs. About stem cells 2017. Available from: http://stemcell.childrenshospital.org/about-stem-cells/.
37. 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(7):822–8.
38. Meisel HJ, Siodla V, Ganey T, Minkus Y, Hutton WC, Alasevic OJ. Clinical experience in cell-based therapeutics: disc chondrocyte transplantation, a treatment for degenerated or damaged intervertebral disc. Biomol Eng. 2007;24(1):5–21.

39. Haufe SM, Mork AR. Intradiscal injection of hematopoietic stem cells in an attempt to rejuvenate the intervertebral discs. Stem Cells Dev. 2006;15(1):136–7.
40. Wyles CC, Houdek MT, Behfar A, Sierra RJ. Mesenchymal stem cell therapy for osteoarthritis: current perspectives. Stem Cells Cloning. 2015;8:117–24.
41. Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. Transplantation. 2013;95(12):1535–41.
42. Saw KY, Anz A, Siew-Yoke Jee C, Merican S, Ching-Soong Ng R, Roohi SA, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial. Arthroscopy. 2013;29(4):684–94.
43. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy. 2013;29(12):2020–8.
44. Peeters CM, Leijs MJ, Reijman M, van Osch GJ, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. Osteoarthr Cartil. 2013;21(10):1465–73.
45. Kuroda K, Kabata T, Hayashi K, Maeda T, Kajino Y, Iwai S, et al. The paracrine effect of adipose-derived stem cells inhibits osteoarthritis progression. BMC Musculoskelet Disord. 2015;16:236.
46. Yousefifard M, Nasirinezhad F, Shardi Manaheji H, Janzadeh A, Hosseini M, Keshavarz M. Human bone marrow-derived and umbilical cord-derived mesenchymal stem cells for alleviating neuropathic pain in a spinal cord injury model. Stem Cell Res Ther. 2016;7:36.
47. Venturi M, Boccasanta P, Lombardi B, Brambilla M, Contessini Avesani E, Vergani C. Pudendal neuralgia: a new option for treatment? Preliminary results on feasibility and efficacy. Pain Med. 2015;16(8):1475–81.
48. Waterman RS, Morgenweck J, Nossaman BD, Scandurro AE, Scandurro SA, Betancourt AM. Anti-inflammatory mesenchymal stem cells (MSC2) attenuate symptoms of painful diabetic peripheral neuropathy. Stem Cells Transl Med. 2012;1(7):557–65.
49. Lui PP. Stem cell technology for tendon regeneration: current status, challenges, and future research directions. Stem Cells Cloning. 2015;8:163–74.