Techniques in Vascular and Interventional Radiology

Biologics

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Biologics are a growing field that has shown immense promise for the treatment of musculoskeletal conditions both in orthopedic sports medicine and interventional pain management. These procedures utilize injection of supraphysiologic levels of platelets and growth factors to invoke the body's own inflammatory cascade to augment the healing of many bony and soft tissue conditions. While many patients improve with conservative care, there is a need to address the gap between those that improve with rehabilitation alone and those who ultimately require operative management. Orthobiologic procedures have the potential to fill this void. The purpose of this review is to summarize the basic science, evidence for use, and post-injection rehabilitation concepts of platelet-rich plasma (PRP) and mesenchymal stromal cells (MSCs) as they pertain to joints, tendons, ligaments, and the spine.
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Basics of Biologics

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an orthobiologic agent defined as a platelet concentration of at least 1,000,000 platelets/μL in 5 mL of plasma and contains a 3- to 8-fold increase in platelet concentrations from baseline.[1] While intially used in oral maxillofacial and cardiac surgery throughout the 1980s and 1990s,[2,3] its application has been increasingly utilized in the field of orthopedics to treat a variety of joint, tendon, and ligamentous injuries. Following a blood draw of autologous blood, centrifugation is performed to separate the blood components into different layers: red blood cells precipitate to the bottom, the middle layer is composed of white blood cells and platelets,[4] and the remaining plasma (platelet poor plasma) forms the top most layer. We isolate this buffy coat layer, termed PRP, with goals of utilizing its composition of supra-physiologic levels of platelets, growth factors, and cytokines to modulate the inflammatory response and accelerate the healing process.[5] Notable cytokines released from platelet alpha granules that are involved in the healing process include platelet-derived growth factor, tissue growth factor-β1, vascular endothelial growth factor, epidermal growth factor,[6] basic fibroblast growth factor, and insulin-like growth factor.[7]

While all platelet concentrations above physiologic levels of 150,000-350,000 μ/L are considered PRP, commercial PRP kits can produce concentrations from 0.52× to 9× baseline levels depending on the kit used. The ideal concentrations for specific pathologies remain an area for needed research, but available literature suggests concentrations of 2.5× to 6× baseline may be ideal,[8-10] with concentrations greater than 10× showing potentially slower healing.[10] PRP preparations are further categorized into leukocyte rich PRP, defined as a leukocyte concentration above baseline, and leukocyte poor PRP, defined as a leukocyte concentration below baseline.[11] Overall, multiple variables relating to the PRP product, including platelet concentration, the presence or absence of leukocytes and erythrocytes, as well as the activation status of the platelets are suspected to play a role in the success of the procedure.[5] The clinical ramifications and cellular effects of these different PRP preparations are still yet to be fully determined.[11]

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Limitations to Reading PRP Literature

Benchtop research studies have consistently shown the beneficial effects of PRP, but the efficacy of PRP in clinical trials has been mixed. Interpreting the clinical literature is challenging given several factors that should be taken into consideration, including sample size, what was injected, how was it injected, and dosage. The specific composition of PRP can vary from person to person and can also be influenced by patient-specific factors (ie, gender, medications taken) and commercial system used to make the PRP.[12-16] The correct dose of PRP is not known and likely varies by target tissue. In a systematic review of PRP literature from 2017, final platelet composition was commonly unreported, specific composition of PRP was only reported in 16% of studies, and clear preparation protocol was noted in only 10% of studies, which makes interpretation of these studies difficult.[17] In addition, autologous conditioned plasma[14] is a platelet concentration that is 1.5-3 times increase in platelet concentration, and while not meeting the threshold of PRP defined as a 3- to 8-fold increase in platelet concentration,[1] it is often confounded with PRP in the literature. The multitude of variables that may affect PRP composition makes it essential that future clinical trials define these attributes so we can make valid conclusions or comparisons regarding its effectiveness. Several attempts have been made to create a standardized classification system for future PRP research, however, no system has been validated and no consensus has been reached.[5,14,4,18]

Mesenchymal Stromal Cells

Another type of orthobiologic agent, mesenchymal stromal cells (MSCs), can be isolated from a variety of tissues, including bone marrow aspirate, adipose tissue, umbilical cord blood tissue, and synovial tissue.[19] While initially the term "mesenchymal stem cells" was coined by Arnold Caplan in 1991 due to the belief that these cells could give rise to bone, ligaments, tendons, and cartilage among other structures[20]; it is now recognized that in vitro isolated MSCs are not a homogenous population of stem cells[21] and thus the name "medical signaling cells," as proposed by Caplan, or "mesenchymal stromal cells" is a more accurate description.[22] The first application of MSCs in orthopedics occurred in the 1970s when bone marrow allografts demonstrated efficacy in reversing osteonecrosis and osteopetrosis in murine models[23-25] and translated to humans by Hernigou et al. in 1997 with the reconstruction of an osteonecrotic humeral head following human leukocyte antigen compatible bone marrow.[26]

The first source of MSCs identified and most commonly used in orthopedic conditions is those from bone marrow aspirate concentrate (BMAC).[27] BMAC preparations are typically harvested from the iliac crest and then centrifuged to concentrate the aspirate to contain MSCs, hematopoietic stem cells, platelets, and cytokines, including platelet-derived growth factor, transforming growth factor-b, interleukin-1 receptor antagonist, and bone morphogenetic proteins 2 and 7.[28] These bone marrow derived cells can either be non-cultured or cultured in vitro, with noncultured autologous cells being the only permitted use by the Food and Drug Administration in the United States at this time.[29]

Another common source of MSCs used in the treatment of orthopedic conditions is adipose-derived stromal cells (ASC). ASCs can be harvested in one of 2 ways. The first, involves washing the adipose tissue, enzymatically digesting the extracellular matrix, neutralizing and re-washing the suspension and then centrifugation, yielding a stromal vascular fraction[30] that can be resuspended and expanded in culture.[31] The second, is via micro-fragmentation which involves lipoaspiration with subsequent washing, rinsing, resizing, and reshaping the lipoaspirate without enzymatic digestion. The proposed mechanism of action of ASCs is that they can support the repair of tissue through secretion of cytokines and growth factors in a paracrine manner similar to bone marrow derived MSCs. ASCs may also have the benefit of releasing antioxidants and free radical scavengers in the area of the injectate to optimize the local environment for cell survival.[31] Of note, any method involving cultural expansion of cells or anything greater than "minimal manipulation," such as enzymatic digestion, is not currently approved by the Food and Drug Administration.

Evidence for PRP

Evidence for Use of PRP in Joints

The majority of the literature on PRP injections for joint pathology is on knee osteoarthritis (OA), with fewer studies on hip OA. There are no studies on PRP injections for shoulder OA, and only case reports or case series for other joints (ie, first carpometacarpal, ankle, etc). PRP is thought to promote cartilage repair when used with an appropriate scaffold for osteochondral defects, although the basic science is still in its early stages.[32,33] In osteoarthritic joints, PRP has been shown to induce chondrocyte proliferation, synoviocyte production of HA, and decreased apoptosis.[34,35] The reduction in pain experienced by patients may be explained by downregulation of the inflammatory cascade.[34,36] The majority of randomized controlled trials (RCTs) in knee OA have compared PRP to hyaluronic acid. A systematic review of 11 RCTs on biologic therapies for the management of knee OA by Delanois et al. found the majority of studies reported PRP improved pain and/or function when compared to control.[36] However, there are limitations to the current literature, including small sample sizes, short-term follow-up, variations in controls and outcome measures, inconsistent dose or number of PRP injections, and differences in the severity of knee OA. These differences make interpreting the literature challenging, however the literature suggests that mild to moderate OA generally has better outcomes.[37-42] Only 4 RCTs of PRP injections for hip OA have been reported, and results have been conflicting. All of the studies compare PRP to hyaluronic acid.[43-46] While Dallari et al. found significant short-term improvement in pain with PRP at 2 and 6 months, there was no difference when compared to HA at 12 months.[44] The other 3 studies failed to find differences between the PRP and HA groups.[43,45,46] There is suggestion

that PRP may have different effects depending on the joint injected, but further research is needed to confirm current findings that outcomes are more favorable in knee OA compared to hip OA.

Evidence for PRP Use in Tendons/Ligaments

PRP and ACP have been used to treat tendon and ligament pathology throughout the body. Several in vivo studies have demonstrated the effects of PRP on tendons, including tendon cell proliferation, increased tenocyte growth factors, and total collagen synthesis.[6,47,48] Despite promising results in basic science and clinical research, a lack of standardization and heterogeneity of PRP used in clinical studies makes it difficult to make definitive conclusions.

However, advances in the understanding of the pathophysiology of degenerative chronic tendon injuries have increased the interest in PRP. There have been a growing number of RCTs studying PRP in tendinopathy, but analyzing clinical efficacy of PRP for tendinopathy remains challenging. Six systematic reviews published between 2010 and 2014 evaluating the same data reported contrasting conclusions on the effectiveness of PRP in tendinopathy.[49-54] A systematic review by Fitzpatrick et al. found that the outcomes of studies are likely dependent on the method of preparation of PRP and found strong evidence for PRP use under ultrasound-guidance.[55]

The majority of RCTs have looked at the role of PRP for lateral epicondylitis and rotator cuff pathology, comprising 70.3% of the 37 RCTs in the literature.[56] Treatment of lateral epicondylitis with PRP has been compared to operative and nonoperative interventions including corticosteroid injections, dry needling, and arthroscopic debridement.[57-60] Arirachakaran et al.'s systematic review and network meta-analysis of 10 randomized controlled trials found that PRP was superior to autologous blood and corticosteroid injections at reducing pain with lower rates of complications.[61] A meta-analysis by Chen et al. concluded that PRP may provide symptomatic relief in the short (<6.5 months) and long-term (>1 year) for lateral epicondylitis, but not all trials have demonstrated a positive benefit.[56] When comparing PRP to arthroscopic debridement, both treatments have been found to be safe and effective. The results of a retrospective chart review comparing PRP to surgical release of the extensor tendon origin suggested that PRP is a suitable alternative to surgical intervention with comparable rates of pain resolution and return to work.[62] Karaduman and colleagues suggested in their retrospective study that PRP showed a greater reduction in pain than with surgery in the short and mid-term, but a prospective study by Merolla et al. comparing arthroscopic debridement and PRP found similar pain reductions at 1-year, but better pain scores in the arthroscopy group at the 2-year follow-up.[60,63]

Most studies published exclusively on PRP for rotator cuff tendinopathy and tears are low-powered studies, which limit their clinical utility. Recent systematic reviews have come to different conclusions on the efficacy of PRP in managing pain with rotator cuff pathology.[56,64] Care should be taken when reviewing the literature to distinguish between the use of PRP to augment arthroscopic rotator cuff repair and PRP injections for rotator cuff pathology. Results with PRP used as augmentation of rotator cuff repairs are inconsistent.[65,66] PRP injections for rotator cuff tendinopathy and tears have likewise shown inconsistent results. The nature of the rotator cuff disease, use of landmark or ultrasound-guidance, number of PRP injections (single versus multiple), and PRP preparation varied across the studies. In addition, not all studies targeted the tendon tear with the PRP injection, with some studies intentionally injecting the subacromial space or glenohumeral joint.[67-72] Further clinical investigations are needed to better define the role of PRP in rotator cuff pathology.

There is also promising high level data supporting the use of PRP for greater trochanteric pain syndrome/gluteal tendinopathy. A randomized controlled trial from Fitzpatrick and colleagues comparing PRP to corticosteroid injection in patients with chronic gluteal tendinopathy showed significantly better improvements in pain and function with a single intratendinous PRP injection versus corticosteroid injection. These improvements were sustained at 2-year follow-up.[73] Furthermore, a recent systematic review from Walker-Santiago et al. determined PRP to be a safe and effective alternative to surgery in patients with recalcitrant greater trochanteric pain syndrome.[74]

PRP appears to be a safe and potentially viable conservative treatment option for patients with tendon or ligament pathology.[75] While the majority of the clinical research has focused on lateral epicondylitis and rotator cuff pathology, PRP has also been reported for the treatment of other tendon and ligament pathology, including: medial epicondylitis, gluteal tendinopathy, hamstring tendinopathy, patella tendinopathy, Achilles tendinopathy, plantar fasciopathy, chronic ankle and syndesmotic sprains, and ulnar collateral ligament tears.[75-79,11]

Evidence for Use in Spine

In the spine, PRP has been used to treat zygapophyseal (facet joint), nerve root, sacroiliac joint, and intervertebral disc pathology, but the majority of studies are on PRP injections for intervertebral disc disease. The results of in vitro and in vivo studies looking at the effects of PRP on intervertebral disc degeneration are promising. PRP has been shown to stimulate cell proliferation and extracellular matrix metabolism, and the anti-inflammatory and anti-apoptotic effects of PRP may facilitate disc repair and symptom relief.[80-84] Disc height and disc hydration have also improved with PRP in an in vivo animal model.[85]

The clinical literature on PRP for discogenic pain is limited to 6 studies, including 3 case reports or case series, 2 prospective trials, and one double-blind randomized controlled trial.[84,86-90] Tuakli et al.'s randomized controlled trial showed improvement in pain scores at 2 years, but at the 2-month mark 83% of the control group crossed over resulting in a single group cohort that could no longer be compared to a control.[88] In addition, there was a high risk for attrition bias with 23 of 47 patients lost to follow-up at 1 year.[91] More high-quality studies are needed to recommend its regular use.

The effects of PRP on zygapophyseal joint pain have been evaluated in one case series, one prospective study, and one

randomized controlled study.[92,57,93] After confirming the short-term benefits of PRP on lumbar facet joints in their prospective cohort study, Wu et al. performed a RCT comparing PRP to steroids.[82,83] Both PRP and steroids relieved pain in the short term, but the therapeutic effects of PRP lasted longer.[93] The literature on the treatment of SI joint pathology with PRP is likewise limited.[94] One randomized controlled trial by Singla et al. showed that PRP injections for SI joint pathology were superior to steroid injections at 3 months postinjection, albeit with a mild increase in complications such as post-injection pain and stiffness.[95,96] PRP has scarcely been evaluated as an epidural treatment of back pain, with only one pilot study reporting positive results.[97]

Evidence for MSC

When looking at the body of evidence supporting MSC use in musculoskeletal conditions, BMAC is the most common source of MSCs in orthopedic literature. Hernigou et al. first published on the use of BMAC for treatment of osteonecrosis (ON) of the femoral head in 1997[26] and this remains one of the few areas of study in the literature with level I evidence for use of MSCs. Though a handful of studies showed equivocal results,[98-100] the majority of publications do support the use of BMC for treatment of femoral head ON, particularly in stage I or II disease.[101-107] There is also some lower level supporting literature for the use of BMAC in post-traumatic avascular necrosis of the talus showing longer duration of survival before collapse or arthrodesis than core decompression alone.[108] No clear efficacy has been shown with AVN of the humeral head.[109]

MSC use for the treatment of osteoarthritis is another area with emerging evidence. In their small RCT comparing BMAC to saline control in patients with knee OA, Shapiro et al. showed a significant improvement in pain, however, there was no significant difference between groups[110] and no regenerative benefits were observed on cartilage sequence MRI at 12-month follow-up.[111] Several other trials have also shown improvements in pain and functional outcomes in patients treated with BMAC for knee OA.[112-114] Mautner, Bowers, and colleagues reported no differences in functional outcomes when comparing micro-fragmented adipose tissue and BMAC injections for knee OA.[115] It has been suggested that those with early to moderate stages of OA may receive more benefit than those with higher grade changes[116] and higher dosage of total nucleated cells have shown to have superior results.[117] While evidence is more limited with hip OA[118] and glenohumeral joint OA[119] compared to the knee, it is noted that patients under 55 had better outcomes in regard to hip OA.[118]

Studies evaluating the use of BMAC for augmentation of surgical treatment of osteochondral lesions of the talus and knee have also shown promise. A recent systematic review by Chahla et al. demonstrated that BMAC had a good effect for large cartilage lesions (>3 cm^2) and improved outcomes with those patients less than 45 years old, smaller cartilage lesion size, and fewer number of lesions.[120] Evidence for the use of BMAC for osteochondral lesions in the talus is supported primarily as an augmentation with surgery, but more research is needed given the highly heterogeneous indications for these studies and lack of studies evaluating BMAC use alone.[121-124]

Regarding treatment of tendon pathology, one study to date shows promising results for treatment of lateral epicondylitis with BMAC injection in a case series of 30 patients with significant improvements in outcomes at 6 weeks post-procedure.[125] BMAC augmentation of surgical rotator cuff repair at 10-year follow-up demonstrates superior outcomes to surgical repair alone, and those patients with higher cell counts at the time of augmentation showed greater tendon integrity at long-term follow-up.[126] A recent cross over study looking at BMAC versus exercise therapy for greater than 50%, partial rotator cuff tears showed significant differences in pain, reported outcomes, and function over therapy at 6 months as well 89% overall improvement at 2 years.[127]

For applications in the spine, the majority of studies investigate the use of cultured MSCs for intradiscal treatment. Pettine et al. showed improvements in pain and function in a case series of patients with discogenic low back pain treated with percutaneous intradiscal BMC injection with follow-up data reports at 12, 24, and 36 months.[128-130] At final follow-up, data were consistent with studies in other regions showing a positive dose-response correlating with the number of cells injected.[130] A summary of intradiscal studies to date can be seen in the Table.[131]

Though the evidence for the use of MSCs for musculoskeletal pathology is promising, there remains the need for continued investigation via multi-center, well powered randomized controlled trials.

Rehabilitation Post-injection and Expected Outcomes

The literature on rehabilitation protocols after PRP and MSC injections for tendon/ligament, joint, and spine pathology is limited and there is a paucity of evidence to help guide clinicians, despite knowing that rehabilitation is an integral part of healing for many other musculoskeletal disorders. Attempts have been made to catalogue variables in the rehabilitation period, but most guidelines are based on expert recommendation at this time.[132,133] One common entity among rehabilitation guidelines following these orthobiologic procedures is an understanding of the healing cascade to guide progression back to return to sport. Common features of orthobiologic rehabilitation protocols for tendinopathy include a short period of weight bearing restriction, nonspecific activity restrictions for 1-2 weeks, range of motion exercises within 1-2 weeks following the injection, strengthening program beginning 2 weeks after injection, and initiating dynamic loading/plyometrics at 6-8 weeks postinjection.

Understanding of the tissue healing process comes mostly from animal studies, from which 3 phases of the healing cascade are commonly described: inflammatory, proliferative, and remodeling phases.[134-136] The first phase is the inflammatory phase which lasts between 4 and 7 days, during which inflammatory cells such as monocytes and macrophages enter the site of injury and clean up damaged tissue

Table [131]

Table 8. *The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Noriega et al, 2017 (283) Sample size = 24 Follow-up = 12 months RCT	24 patients with chronic low back pain with lumbar disc degeneration and unresponsive to conservative treatments were randomized into 2 groups. Patient age (yrs) mean age ± SE = 38±2 s	Allogeneic bone marrow MSCs by intradiscal injection or a sham infiltration of paravertebral musculature with anesthetic	The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 X 10, 6 cells per segment under local anesthesia	VAS, ODI, MRI, SF-12	• MSC-treated patients displayed a quick and significant improvement in all algofunctional indices versus the controls. • Both lumbar pain and disability were significantly reduced at 3 months and improvement was maintained at 6 and 12 months. Overall there was an average 28% improvement in pain and disability one-year after the intervention. • Only 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement.	• 28% improvement in all patients • 40% of patients perfect result • Positive result
Pettine et al, 2015, 2016, 2017 (253,280,281) Sample size =26 Follow-up=3 years Prospective, open-label, non-randomized, 2-arm study	26 patients presented with symptomatic moderate to severe discogenic low back pain Patient age (yrs)= 18–61 years (median 40)	Autologous bone marrow concentration (nonexpanded)	2–3mL of bone marrow concentrate was injected in lumbar disc (1.66_106/mL)	ODI, VAS, and MRI	• The average ODI and VAS scores were reduced to 22.8 and 24.4 at 3 months. After 36 months, 6 patients proceeded to surgery. • After 36 months, 20 of the 26 patients reported average ODI and VAS improvement to 17.5 ± 32 and 21.9 ± 4.4 respectively. • One year MRI indicated 40% of patients improved one modified Pfirrmann Grade and no patient worsened radiographically.	• At 36-month follow-up, 6 of 26 patients progressed to surgery. The remaining 20 patients (77%) reported significant ODI and VAS improvements. • Authors concluded that there were no adverse effects and the study provided evidence of safety and feasibility of intradiscal BMC therapy.
Coric et al, 2013 (272) Sample size =15 Follow-up=1 year Prospective cohort	15 patients with single-level, symptomatic lumbar DDD from L-3 to S-1 and medically refractory low back pain Patient age (yrs)= 19–47 years (median 40)	Expanded allogeneic juvenile chondrocyte cells	Mean 1.3mL (1–2 mL, 107/mL) cells solution was injected in the center of the disc space	ODI and NRS scores, 36-item Short Form Health Survey and MRI	• The mean ODI, NRS, and Short-form-36 physical component summary scores all improved significantly from baseline • Ten (77%) of these 13 patients exhibited improvements on MRI. Of these, the HIZ was either absent or improved in 8 patients (89%) by 6 months • Of the 10 patients who exhibited radiological improvement at 6 months, findings continued to improve or were sustained in 8 patients at the 12-month follow-up • Only 3 patients (20%) underwent total disc replacement by the 12-month follow-up due to persistent, but not worse than baseline, LBP	• The results of this prospective cohort are promising with 77% of patients improving • Positive result
Orozco et al, 2011 (271) Sample size =10 Follow-up=1 year Pilot phase 1 trial	10 patients with degenerative disc disease and persistent low-back pain (>6 months; decrease of disc height >50%;) Patient age (yrs)= 35_7 (mean_SD)	Autologous expanded bone marrow–derived mesenchymal stem cells	23±5X106 autologous expanded BMSCs was injected into the nucleus pulposus area	ODI and VAS scores and MRI	• Patients exhibited rapid improvement of pain and disability (85% of maximum in 3 months) that approached 71% of optimal efficacy • This study confirmed feasibility and safety with identification of strong indications of clinical efficacy	• Authors concluded that MSC therapy may be a valid alternative treatment for chronic back pain caused by degenerative disc disease. • They also concluded that advantages over current gold standards include simpler and more conservative intervention without surgery, preservation of normal biomechanics, and same or better pain relief
Kumar et al, 2017 (284) Sample size = 10 Follow-up = 1 year Phase 1 study	10 patients with chronic low back pain lasting for more than 3 months with a minimum intensity of 4/10 on a visual analog scale and disability level ≥ 30% on the Oswestry Disability Index. Patient age (yrs)=between 19 & 70	Combined hyaluronic acid derivative and AT-MSCs	A single intradiscal injection at a dose of 2 X 107 cells/disc (N=5) or 4 X 107 cells/disc (N=5)	VAS, ODI, Short-form 36, lumbar spine x-ray, MRI	• VAS, ODI, and SF-36 scores significantly improved in both groups receiving both low and high cell doses, and did not differ significantly between the 2 groups • At 12-month follow-up 7 patients reported 50% or greater improvement in VAS • 6 patients achieved treatment success with pain reduction of 50% or greater and improvement on disability scores on ODI • Among 6 patients who achieved significant improvement in VAS, ODI, and SF-36, 3 patients were determined to have increased water content based on an increased apparent diffusion coefficient on diffusion MRI	• 60% significant improvement with no adverse effect • Authors concluded that combined implantation of AT-MSCs and hyaluronic acid derivative in chronic discogenic low back pain is safe and tolerable • Positive result
Mochida et al (247) Sample size =9 Follow-up=3 years Prospective clinical study	9 patients with Pfirrmann grade III disc degeneration and posterior lumbar intervertebral fusion. Patient age (yrs)=20-29 years	Autologous cultured nucleus pulposus chondrocytes that cocultured with MSCs	One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery	JOA scoring and MRI	• Clinical outcomes based on Japanese Orthopedic Association (JOA) scoring system for low back pain showed significant improvement from 14.2 ± 4.8 points preoperatively to 27.2 ± 1.6 points at 3 years after transplantation of the activated NP cells (maximum possible score of 29 points) • The JOA scoring system also showed improvement in low back pain subscale from 1.2 ± 0.5 points preoperatively to 2.7 ± 0.2 points at 3 years after the transplantation with maximum possible score of 3 points for no pain • No adverse effects were observed during the 3-year follow-up period	• Significant improvement in function and pain scores was reported • This study confirmed the safety of activated NP cell transplantation, and the findings suggest the minimal efficacy of this treatment to slow the further degeneration of human intervertebral discs

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Meisel et al, 2006 (273) Sample size =12 Follow-up=2 years	Patients with discogenic pain after repeat discograms. Patients were treated with cell therapy at least 3 months post the endoscopic. Patient age (yrs)= 18–75 years	Autologous cultured disc-derived chondrocytes (from surgical treatment of their disc prolapse)	Cells are injected into disc approximately 12 weeks following discectomy. The cell dose was not mentioned	ODI and VAS scores and MRI	• The median total Oswestry Score was 2 in the autologous disc chondrocyte transplantation (ADCT) group compared with 6 in the control group. Decreases in the Disability index in autologous disc chondrocyte transplantation (ADCT)-treated patients correlated with the reduction of low back pain • Decreases in disc height over time were only found in the control group, and of potential significance, intervertebral discs in adjacent segments appeared to retain hydration when compared to those adjacent to levels that had undergone discectomy without cell intervention	• Significant improvement • Positive result

RCT = randomized controlled trial; BMSCs= Bone marrow derived stem cells; MSCs=medicinal signaling cells or mesenchymal stem cells; JOA = Japanese Orthopedic Association; MRI = magnetic resonance imaging; NP = nucleus pulposus; DDD=degenerative disc disease; BMC = bone marrow concentrate; LBP=low back pain; NRS = Numerical Rating Scale; ODI = Oswestry Disability Index; VAS =Visual Analog Scale; SD=standard deviation; SF-12=12-item short-form survey; HIZ-high intensity zone; adipose-tissue derived mesenchymal stem cells (AT-MSCs)

Adapted from: Sanapati J, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. *Pain Physician* 2018; in press (29).

components to allow the body to heal.[137] The next phase is the proliferative phase that begins 2-5 days following injury and last up to 8 weeks, where macrophages trigger a release of bioactive factors, such as growth factors that are essential for tissue repair and proliferation.[138] As MSCs arrive to the site of injury and begin differentiating into tissue types, collagen is laid down in a disorganized fashion. Finally, the last phase is the remodeling phase, which begins at around 6 weeks and continues for months after injury.[137] In this stage, collagen formation slows down and tissue begins to remodel to improve its cellular formation and strength.[138]

Due to literature supporting 70% of growth factors from PRP being released within the first 10 minutes after injection, a very short period of immobilization (~10-15 minutes) is often recommended after PRP injections with the idea that there is no loss of PRP to adjacent structures immediately after the injection.[139] While a more recent cadaveric study comparing movement and immobilization did not show this loss of PRP to adjacent structures when dye was injected into the Achilles tendon,[140] it is still common for a short period of immobilization to allow acute paint to subside and avoid any vasovagal episodes.

Given the pain associated with the inflammatory phase following PRP injections, pain control is a priority. However, NSAIDs and cryotherapy are avoided due to their anti-inflammatory nature.[141,133] While many clinicians instruct patients to stop use of NSAIDs 5-7 days prior to procedure and during the inflammatory phase postinjection, there is some evidence in animal models showing NSAIDs started late in the proliferative stage also decreased the biomechanical strength of a repaired tendon.[142]

In the inflammatory phase, most protocols avoid stretching and strengthening of the tendon for protection during this vulnerable period, while promoting range of motion exercises for joint motion to prevent stiffness or contracture.[132] As the proliferative phase begins, strength, and endurance training are added in addition to full range of motion exercises. A progressive strengthening program starting with isometric to concentric then to eccentric exercises is recommended.[132] This is important, especially in tendons, as mechanical stress of the tendons has been found to drive the early stages of tendon repair and to optimize outcomes.[132,143-146] Proprioceptive training may have benefit in joint related pathology, although it is not a common component of existing rehabilitation protocols.[147] As we move into the remodeling phase, strengthening, specifically eccentric exercises, are important to drive tissue remodeling after the 6-8-week mark.[132] As strengthening improves, the rehabilitation protocol can progress to dynamic functional activity, plyometrics, and return to sport programs, although there is no consensus on specific timing to return to sport.[132] We know rehabilitation is a key component to many musculoskeletal conditions and just as protocols have been optimized for these conditions, more research is required to determine the optimal rehabilitation protocols postorthobiologic interventions.

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