Alternative Therapeutic Modalities in Sports Medicine

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Abstract
Bone marrow aspirate, prolotherapy, platelet-rich plasma, and autologous conditioned serum represent alternative treatment options that have emerged to address various musculoskeletal ailments. We have reviewed the basic science, physiology, and clinical evidence of each of these modalities and discovered that each treatment has its individual place in the management of common orthopaedic pathologies. Bone marrow aspirates are successful in treating early arthritis and cartilage defects. Prolotherapy and platelet-rich plasma have demonstrated good efficacy in treating inflammatory processes and early arthritis. Finally, autologous conditioned serum (Orthokine) represents a promising treatment option for chronic joint arthritis. The clinical evidence supporting these alternative treatment modalities is insufficient and further level 1 evidence is needed before we can begin to employ these techniques in our daily orthopaedic practice.

Providers will often employ non-operative treatment regimens (physical therapy, oral anti-inflammatory agents, etc.) to address musculoskeletal and joint pain with the ultimate goals of reducing symptoms, improving function, and obviating the need for surgical intervention. The literature has specifically highlighted the effectiveness of local musculoskeletal injections to address certain conditions such as local inflammatory processes, soft tissue injuries, and early arthritis. These injections often include a corticosteroid mixed with a local anesthetic. Recently, alternative treatment options have emerged to help combat the growing incidence of joint pain and address those pathologies that did not historically gain relief from traditional management approaches. In this review, we will explore four different treatment modalities: bone marrow aspirate injections, prolotherapy, platelet-rich plasma injections, and autologous conditioned serum injections. Specifically, we will review the basic science, physiology, and mechanism of action for each treatment and highlight the recent evidence in the literature that supports or rejects these modalities in the treatment of individual sports medicine pathologies.

Bone Marrow Aspirate Injections
Basic Science and Physiology
In adults, the bone marrow contains a rich reservoir that produces new blood cells, including regenerative cells. Bone marrow aspirate (BMA) serves as a source of mesenchymal stem cells that can be used for the regeneration of cartilage and other tissues of the musculoskeletal system. Typically, the cells are aspirated from the patient’s iliac crest. The cells obtained are undifferentiated, allowing them the ability to replicate themselves into a variety of tissue types.

The stem cells are harvested and prepared as follows: First, a small amount of the patient’s bone marrow is extracted, the contents of which are subsequently placed into...
a centrifuge, which separates the regenerative cells and platelets from the rest of the aspirated bone marrow components. The result is a concentrate that is 5 to 11 times richer in regenerative cells and growth factors. Of note, platelets are usually injected with the stem cells because they contain growth factors that the stem cells need for growth and engraftment.

The potential applications that have been associated with bone marrow aspirate injections include mostly the treatment of symptomatic cartilage defects and cases of early osteoarthritis. Stem cell injections have been compared to autologous chondrocyte implantation given their similar implementation and mechanism of cartilage restoration; however, the stem cell injections are potentially less invasive (performed percutaneously or through a mini open approach), are performed as a one-step procedure, and have a potentially higher proliferative capacity. Conversely, this procedure is not currently covered by insurance and therefore can be costly to the patient.

Clinical Evidence—Cartilage Lesions
Fortier and coworkers compared the outcomes of treatment with BMA combined with surgical microfracture to microfracture alone in the repair of full-thickness cartilage defects in an equine model. Second look arthroscopy and MR imaging at 3-month follow-up revealed improvement in repair tissue in the BMA and microfracture group compared to microfracture alone as well as greater type-II collagen/GAG content and improved orientation of the collagen in BMA and microfracture group on histologic analysis. Saw and colleagues reported greater coverage of full-thickness articular cartilage defects following subchondral drilling treated with BMA and hyaluronic acid (HA) compared to HA alone and their control group (no HA). Histologic analysis demonstrated higher hyaline cartilage in the BMA and HA group. Wakitani and associates transplanted autologous culture-expanded BMA into nine full thickness articular cartilage defects of the patellofemoral joints in the knees of three patients. The BMA was directly injected into the cartilage defects and covered with autologous periosteum. All three patients returned to work by 8 months postoperatively with significantly improved IKDC scores at time of final follow-up.

Clinical Evidence—Osteoarthritis
Koh and coworkers evaluated the clinical outcomes and imaging results of 18 patients (mean age 55 years with an average 2-year follow-up) who received intra-articular injections of autologous mesenchymal stem cells for the treatment of knee osteoarthritis. WOMAC scores decreased significantly from 49.9 points preoperatively to 30.3 points at the final follow-up. Lysholm scores also improved significantly from 40.1 points to 73.4 points. Mean VAS score decreased from 4.8 preoperatively to 2.0 at the time of final follow-up. Additionally, follow-up MRI scores significantly improved from 60.0 points to 48.3 points. Their analysis demonstrated that improvements in clinical and imaging results were positively related to the number of stem cells injected.

In a randomized clinical trial using bone marrow aspirates for meniscus regeneration and osteoarthritis, Vangsness and associates reported an improvement in knee pain and less osteoarthritis progression in the BMA group. The control patients (treated with hyaluronic acid) were 3.5 times more likely to develop degenerative bone changes associated with osteoarthritis, suggesting a decrease in knee osteoarthritis progression with BMA treatment. Varma and colleagues compared the results of arthroscopic debridement alone versus debridement plus BMA injection. In their study, patients in the BMA group demonstrated considerably improved osteoarthritis outcome scores, decreased VAS pain scores, and improved quality of life during the study period and at final follow up.

In conclusion, bone marrow aspirate is comprised of mesenchymal stem cells isolated via the centrifugation of undifferentiated cells that are aspirated from the iliac crest. BMA has been used in the management of early arthritis and the treatment of symptomatic cartilage lesions. Clinical trials have demonstrated efficacy with the benefit of a low side effect profile and minimally invasive implementation. The major downside of the use of bone marrow aspirate is that the treatments can be expensive and are typically not covered by insurance.

Prolotherapy
Basic Science and Physiology
Prolotherapy involves injecting a dextrose solution into an injured ligament or tendon. The high osmolarity of 20% glucose immediately causes a net flow of water out of cells across their cell membranes into the immediate vicinity of the injection site. Cells at the injection site become flaccid and dehydrated and some may eventually die. When cells are osmotically shocked, the integrity of the cell membrane is lost and factors are released which attract granulocytes and other inflammatory mediators to the area. The localized inflammatory response leads to increased blood supply to the area bringing about the flow of nutrients and factors for tissue repair. Eventually, fibroblast cells migrate to the injection site, proliferate, and start depositing new collagen. In addition to dextrose, other substances utilized in prolotherapy injections include lidocaine, phenol, glycerine, and cod liver oil extract.

Prolotherapy is typically injected along distinct tender points at the entheses of tendons or ligaments. Common diagnoses treated include: early joint arthritis, muscle strains, epicondylitis, and Achilles tendinosis. Clinical trials have reported no major side effects with its use. The cost of these injections is approximately $200 per session and are typically not covered by insurance. Most conditions
are typically treated with 4 to 8 injections with 4 to 6 week intervals between visits.

**Clinical Evidence—Osteoarthritis**
Robago and colleagues studied the effects of prolotherapy in 36 participants (60 ± 8.7 years old, 21 female) with moderate-to-severe knee OA who received an average of 4.3 ± 0.7 injections over a 17-week treatment period. Overall WOMAC scores improved 4 weeks after the first injection session (7.6 points, 17.2%) and continued to improve through the 52-week follow-up (15.9 points, 36.1%). Based on their findings, the investigators concluded that in adults with symptomatic moderate to severe knee OA, dextrose prolotherapy may result in safe, significant and sustained improvement of knee pain, function, and stiffness scores.

Reeves and associates analyzed the effects of dextrose prolotherapy on knee OA in patients with more than 6 months of pain and Grade 2 or higher arthritic changes on imaging. Multivariate analysis of paired values at 0 and 12 months revealed a statistically significant improvement in pain, swelling, joint flexion, and joint laxity in the dextrose-treated knees compared to their control group who received lidocaine injections only.

**Clinical Evidence—Inflammation and Tendinosis**
Scarpone and coworkers assessed whether prolotherapy improves elbow pain, grip strength, and extension strength in 24 patients with lateral epicondylitis. In a double-blind randomized controlled trial, pain scores improved in the prolotherapy group compared to controls (saline injection): 4.5 versus 5.1, 0.5 versus 3.5, at 0 and 16 weeks, respectively. Prolotherapy subjects also reported improved extension strength compared to controls and improved grip strength compared to baseline values. Most notably, the clinical improvements in the prolotherapy group subjects were maintained at 1 year. In contrast to Scarpone’s trial, Carayannopoulos and colleagues reported no significant differences in VAS or DASH scores among patients treated with prolotherapy versus corticosteroid injections for chronic lateral epicondylitis. The investigators’ conclusions were that although both therapies were generally well tolerated and appeared to provide some long-term benefit, larger, more controlled trials are warranted for reliable outcomes.

Yelland and associates compared the effectiveness and cost-effectiveness of eccentric loading exercises (ELE) with prolotherapy injections used alone and in combination for painful Achilles tendinosis. VISA-A scores at 12 months were significantly higher for combined treatment versus the exercise group or prolotherapy alone. Additionally, the combined treatment had the lowest incremental cost per additional responder compared with ELE alone.

In conclusion, prolotherapy consists of a dextrose solution that is injected into an injured region resulting in a localized inflammatory response. The increased blood supply to the region and resultant fibroblast proliferation leads to tissue repair and collagen synthesis. Prolotherapy can be utilized to treat inflammatory conditions, such as epicondylitis and tendonitis, as well as early arthritic changes. Clinical trials demonstrate superior efficacy compared to corticosteroid injections for inflammatory conditions and knee arthritis. Prolotherapy has a low side effect profile, a minimally invasive implementation, and can be administered at a relatively low cost to the patient.

**Platelet-Rich Plasma**

**Basic Science and Physiology**
Platelet-rich plasma (PRP) is an autologous concentration of platelets in plasma. The abundance of growth factors present in PRP concentrate theoretically enhances the quality of wound healing and reduces healing time by expediting tissue regeneration. These growth factors have been shown to be directly responsible for increasing cell proliferation, initiating higher collagen production and angiogenesis, and inducing cell differentiation.

PRP starts as a collection of whole blood that is anticoagulated with citrate dextrose before undergoing two stages of centrifugation which separates the PRP aliquot from platelet-poor plasma and red blood cells. Therapeutic PRP concentrates the platelets by roughly five-fold the baseline amount found in blood. The aliquot is then prepared in an anticoagulant state and used on a graft, flap, or wound. Adding autologous thrombin and CaCl₂ triggers the activation process which leads to the secretion of growth factors from the platelet alpha granules. Of note, 95% of all factors are secreted within the first hour.

Currently, the majority of orthopaedic applications for PRP can be grouped into 1 of 4 categories: chronic tendinopathies, acute soft tissue injuries, early arthritis, and intraoperative augmentation. Cell proliferation and total collagen production is increased in human tenocytes cultured in PRP. Additionally, the cytokines contained in PRP have a positive effect on muscle healing. PRP injected in a gastrocnemius contusion injury in a mouse model resulted in accelerated satellite cell activation and increased diameter of regenerating myofibers.

**Clinical Evidence—Inflammation and Tendinosis**
Mishra and coworkers reported decreased pain at 2 years following PRP injections for chronic elbow tendinosis. Sanchez and colleagues reported improved range of motion and early return to activity following Achilles tendon injuries. Monto reported on the treatment of 30 patients with chronic Achilles tendinosis unresponsive to nonoperative modalities who were treated with a single ultrasound guided injection of PRP. Average AOFAS score increased from 34 to 92 by 3 months after PRP treatment and remained elevated at 88 at 24 months post-treatment. Pre-treatment imaging abnormalities present in the Achilles tendon on MRI and ultrasound studies resolved in 27 of 29 patients by 6 months after treatment.
at the effects of a platelet-rich plasma injection in patients with chronic Achilles tendinopathy. In this study, there were no clinical or ultrasonographic superiority of PRP over placebo at 1 year when combined with an eccentric training program. Gosens and coworkers compared the effectiveness of PRP compared with corticosteroid injections in patients with chronic lateral epicondylitis. Baseline VAS and DASH scores were compared with the scores at 2-year follow-up, and both groups significantly improved across time; however, the DASH scores of the corticosteroid group returned to baseline levels, while the DASH scores of PRP group remained significantly improved.

Clinical Evidence—Osteoarthritis

Gobbi and colleagues evaluated the effectiveness of intraarticular PRP injections in active patients with knee OA with or without previous surgical treatment for cartilage lesions. All patients showed significant improvement in all scores at 6 and 12 months and returned to their previous activities. Kon and associates compared PRP versus hyaluronic acid in the treatment of 150 patients affected by cartilage degenerative lesions and early and severe OA. IKDC and visual analog pain scores were improved to a greater extent in the PRP group at the 6 month follow-up. Based on their findings, the investigators concluded that autologous PRP injections showed greater and longer efficacy than hyaluronic acid injections with respect to reducing pain, improving symptoms, and recovering articular function.

Clinical Evidence—Augmentation

The evidence to support PRP supplementation for bone healing is not encouraging. Multiple studies have reported no clinical or functional difference in patients who underwent PRP supplementation to enhance bone healing following lower extremity osteotomies. Additionally, Carreon and coworkers reported higher nonunion rates in patients treated with PRP versus their control group following instrumented posterolateral spinal fusions. Bergeson and colleagues reported that rotator cuff tear rates (56.2% versus 38.1%) were significantly higher when the repairs were augmented with PRP compared to those with no augmentation. Additionally, postoperative functional outcome scores were not significantly improved in the PRP group compared to the control. Rodeo and associates analyzed patients randomized to either receive PRP at the tendon-bone interface compared to a standard arthroscopic rotator cuff repair. They reported no differences in ASES scores, muscle strength, and tendon-to-bone healing between the PRP and control groups. Weber and coworkers demonstrated similar results with no significant difference in VAS scores, narcotic use, recovery of motion, SST, or ASES scores following arthroscopic rotator cuff repair with or without PRP augmentation.

In conclusion, PRP consists of an autologous concentration of platelets in plasma that contains an abundance of growth factors. The orthopaedic applications for PRP include: chronic tendinopathies, acute soft tissue injuries, early arthritis, and intraoperative augmentation of bone and soft tissue repairs. Clinical trials demonstrate good efficacy in treating tendinosis and tenonopathy, yet discouraging results when used to enhance bone and soft tissue healing following surgical repair (e.g., osteotomy and rotator cuff repairs). Treatments have a low side effect profile and a minimally invasive implementation, however, can be expensive for the patient as it is typically not covered by insurance.

Autologous Conditioned Serum (Orthokine and Regenekine)

Basic Science and Physiology

Autologous conditioned serum (ACS) consists of individual autologous proteins that are derived from the patient’s blood and then applied as a medication. Interleukin-1 (IL-1) plays a key role in the pathology of osteoarthritis and subsequent joint pain. It induces an inflammatory response and in chronic conditions can lead to the eventual destruction of articular cartilage. The biological antagonist, interleukin-1 receptor antagonist (IL-1Ra), which is naturally present in the bloodstream, intervenes in the pathologic mechanism by binding to the IL-1 receptor and blocking IL-1 from docking.

The method for making ACS was developed by Dr. Julio Reinecke and Dr. Peter Wehling in Germany. First, blood is drawn via a special syringe. Next, glass beads in the syringe induce the white blood cells to synthesize increased protective proteins (IL-1Ra) within the incubated venous blood. The incubator mimics body temperature creating an optimum environment for protein synthesis. Finally, a centrifuge separates the amber serum from blood clot (serum contains high concentration of protective and regenerative proteins).

ACS can be used to treat osteoarthrosis and joint pain throughout the body. Typically, a patient will receive three to six injections into the affected joint as part a single treatment regimen. ACS contains up to 30 times higher concentrations of IL-1Ra than what is found in normal blood. The goal of this treatment modality is to address the underlying pathomechanism of OA as it relates to inflammation.

Clinical Evidence—Osteoarthritis and Joint Pain

Yang and coworkers reported on 167 patients who received either 6 intra-articular injections of ACS or saline as a control. Both groups experienced similar improvements in WOMAC scores (16.8% versus 16.5%). ACS resulted in significantly greater improvement in the Knee Injury and Osteoarthritis Outcome Score system sport parameters versus the control group. The ACS group reported lower visual analog pain scores; however, this was not statistically significant. The investigators concluded that ACS shows promise, however, did not meet primary efficacy objective of 30% superiority in WOMAC index.
leagues analyzed 376 patients with knee OA in a prospective, randomized, double-blinded, placebo-controlled trial using an intention-to-treat analysis.47 The effects of ACS were significantly superior to those of HA and saline for all outcome measures (Western Ontario and McMaster Universities osteoarthritis index, global patient assessment, visual analog scale, and Short-Form 8) at all-time points.47 Adverse events were comparable between ACS and saline groups and higher in the HA group.47 The investigators’ results demonstrated that treatment with ACS results in a significantly better therapeutic effect compared to HA and saline not only at 6 months, but also out to 2 years of follow-up.47

Clinical Evidence—Muscle Injuries
Wright-Carpenter and associates conducted a study on muscle strain injuries in professional athletes receiving either ACS or a standard anti-inflammatory treatment as the control group.48 Recovery time was significantly shorter in the ACS group (16.6 days) compared to the control group (22.3 days).48 Furthermore, MRI analysis supported the observed acceleration in recovery time in the ACS group.48

In conclusion, autologous conditioned serum consists of the patient’s own blood that is extracted, manipulated, and then reintroduced to the body as an anti-inflammatory medication (high concentration of IL-1Ra). Clinical trials demonstrate good efficacy in treating knee arthritis and muscle strains compared to hyaluronic acid and placebo treatments. It represents a promising treatment option for chronic joint arthritis with a low side effect profile and minimally invasive implantation; however, it is still considered an experimental treatment that is only available in select clinics at a high cost to the patient.

Conclusion
All of the treatment modalities reviewed demonstrated some efficacy in the treatment of common sports medicine pathologies. Although these treatments can be expensive, they represent an alternative to standard nonoperative management methods while maintaining a low side effect profile.10,11 As the supporting data is currently sparse in the orthopaedic and sports medicine literature, we encourage further clinical studies with level 1 evidence before sound recommendations can be made regarding the use of these alternative techniques for our patients.

References


