

Mini Review

Orthobiologics: A New Frontier for Musculoskeletal Disease

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Received: July 04, 2014; **Accepted:** Aug 04, 2014;

Published: Aug 06, 2014

Keywords

Orthobiologics; PRP; BMC; Adipose-derived Stem Cells; Umbilical Cord-derived Cells

The past 20 years of medicine has seen an unprecedented rate of scientific discovery, providing a greater understanding of disease pathology and processes, eliciting a new area of medicine called “Orthobiologics”. Orthobiologics have a specific emphasis on tissue healing and biological restoration by harnessing the regenerative potential within the body’s own cells and redirecting their use for accelerated healing in damaged or diseased tissues. In the field of Sports Medicine, Orthobiologics have prompted a paradigm shift in treatment; from temporary symptomatic management to delay or disease prevention by modifying cell signals within the biologic environment. Many cellular therapies are evolving as a bridge between conservative non-invasive options and invasive surgical treatments. Thus far, Orthobiologics have experienced three generations of evolution, beginning with visco supplementation, or Hyaluronic Acid, progressing to Platelet Rich Plasma [1] and Bone Marrow Concentrate. Recent reports of Adipose and Umbilical Cord Derived Cells and specific growth factors such as BMP 7 [2] are now also found in the literature.

First generation Orthobiologics were available in the clinic in 1997 and consisted solely of Hyaluronic Acid (HA), a viscosupplementation for joint arthritis. HA reduced painful symptoms of osteoarthritis in those patients who responded to treatment and provided a superior safety profile when compared to continuous NSAID use for pain control [3-5].

Platelet Rich Plasma (PRP) didn’t appear in the sports medicine literature until 2006; however, this 2nd generation of Orthobiologics was actually first used by Ferrari et al in 1987 following open heart surgery [6]. PRP was the first autologous Orthobiologic and used previously in many therapeutic areas including ENT, maxillofacial surgery, ophthalmology, urology, dentistry, cosmetic and neurosurgery as well as wound healing. Scientists studying wound healing discovered that platelets were not solely involved in clotting, but that they contained several bioactive proteins, such as stromal-derived factor 1 α , as well as growth factors like TGF β -1, IGF-1, bFGF, BMP-2, etc., which encourage regenerative potential and healing properties [7,8]. Theoretically, the potent concentration of platelets are administered to stimulate a supra-physiologic response, as they are comprised of an undifferentiated cocktail of anti-inflammatory, pro-inflammatory, anabolic, and catabolic mediators in an attempt to elicit the body’s natural healing response. Although, most of the literature consists of small case series [9,10], larger randomized controlled trials have demonstrated superior efficacy in areas such as tendinopathies [11,12] and knee osteoarthritis [13-16]. The authors recently published results of a multicenter, blinded controlled trial on leukocyte rich PRP use for lateral epicondylitis. Success rates for patients at 24 weeks post-treatment were 83.9% in the PRP group compared with 68.3% in the control group (P = .037) [11]. More recently, biologic injections have been applied to the spine. Prospective double blind randomized controlled data from the Hospital of Special Surgery (HSS) demonstrated improved outcomes with intra-discal PRP [17]. PRP injections for facet mediated joint pain have previously been described although warrants further clinical trials [18]. PRP applications will continue to expand with the growing volume of literature and mainstream publicity from PRP use in professional athletes; albeit, consistent guidelines for the variety of applications remain lacking. Standardization for optimal outcomes is needed to clarify which PRP preparation and protocol variables are best for which musculoskeletal conditions.

Bone Marrow Concentrate (BMC) is considered the 3rd generation of Orthobiologic therapy. See Figure 1. It has a potent mixture of mesenchymal stem cells (MSCs), hematopoietic cells, platelets, and cytokines noted for possessing anti-inflammatory, immunomodulatory, and chondrogenic properties, which act as the foundation for its regenerative potential [19]. Although the exact mechanism is unknown, it is hypothesized that the bone marrow concentrate milieu either induces differentiation and proliferation of resident stem cells, or possesses innate chondrogenic potential [19]. Dr. Caplan recently lectured at the 2014 (TOBI) The Orthobiologic Institute regenerative medicine symposium, suggesting that perivascular cells or Pericytes, adhere to blood vessels and act as one of our body’s largest reservoirs for Mesenchymal Stem Cells. He explained that when the body undergoes trauma, soluble factors within the perivascular space cause the release of Pericytes from



Figure 1: Harvesting of Bone Marrow Concentrate (BMC).

microvessels. Pericytes act as “Medicinal Signaling Cells” once released, where they can be activated into Mesenchymal Stem Cells, exhibiting trophic, immunomodulatory, and osteogenic roles. Dr. Caplan’s research continues to expand our understanding of MSCs and provides insight into the potential therapeutic mechanisms of Mesenchymal Stem Cells [20].

The primary author recently presented clinical outcomes using BMC. 125 patients received hip, single knee, bilateral knees, shoulder, ankle, or cervical spine BMC injections. 87 patients had both pre- and post- injection pain scores available for review, of which 71% demonstrated a statistically significant reduction in overall pain at a median, follow up of 148 days. When comparing 87 with pre-post pain (complete) vs. 38 with pre or post missing (incomplete) data, there was no evidence of selection bias as both groups had similar variables (age, BMI, f/u time, satisfaction etc). Comparing statistically significant results from all treated regions revealed the single knee and bilateral knee injections had the largest improvement in pain score. Furthermore, 92% of patients reported satisfaction with the procedure and 95% of patients would recommend the procedure to a friend. Contrary to prior reports in the literature of an inverse relationship, age had no correlation with outcomes in this cohort of patients up to 79 years of age reporting positive results [21]. BMC therapy is also being used as an adjunct therapy post-operatively for procedures such as arthroscopic debridement, meniscal transplantation and subchondroplasty. Based on historical controls without use of BMC as an adjunct therapy, improved surgical results have been observed when a patient undergoes BMC treatment 2-3 weeks postoperatively [19].

Compared with BMC, adipose-derived MSCs, ADMSCs, are procured in much larger quantities with less invasive methods. ADMSCs continue to chondrogenic, osteogenic, adipogenic, myogenic, or neurogenic lineages. They have enhanced rates of proliferation, but show lesser responses to TGF- β -induced chondrogenesis [22]. Nevertheless, because of their facile procurement the use of ADMSCs is now being explored for various musculoskeletal applications.

In contrast with bone marrow or adipose-derived cells, umbilical cord-derived cells, UCDCs, have reduced isolation efficiency but

expansion is more effective. Animal models using UCDCs triggered an inflammatory reaction in the synovium²³; yet, there is a clinical trial at Rush University using UCDCs to treat cartilage defects. The results of this trial are anticipated.

To date, there is a paucity of level I evidence evaluating the therapeutic efficacy of BMC, as many of the studies are non-randomized, lack a control, and present only observational results of case series. Properly powered clinical trials and clinician collaboration is needed to further elucidate BMC as the 3rd generation of Orthobiologics and follow-up further on the use of ADSCs and UCDCs. Many queries remain polemical such as the ideal cell harvest technique, cell preparation as well as optimal window for various indications and injection protocols. Increased clinical use must not precipitate the responsibility to publish data and improve our understanding with controlled clinical trials. These early autologous therapies may serve as an introduction for more customized, refined cellular therapies incorporating the use of appropriate biomarkers to acquire knowledge of the mechanism of action as well as the optimal method of treatment.

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