CHAPTER 16

Education and Standardization of Orthobiologics: Past, Present & Future

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SUMMARY

Since the beginning of Orthobiologics, the field has continued to evolve and grow, creating a preliminary framework for clinical application in musculoskeletal injuries. With increasing demand from an aging population, and numerous physicians incorporating the techniques into their existing practice, Orthobiologics have started to develop into almost a subspecialty of their own. However, the boom of Orthobiologics has not been matched with an equal surge in high level of evidence studies, leaving much of the field under researched. To date, four generations of Orthobiologics have been identified: Hyaluronic acid (HA), Platelet rich plasma (PRP), Bone marrow concentrate (BMC), and Adipose derived mesenchymal stem cells (aMSC). Although research is limited throughout the field as a whole, larger randomized trials are emerging for the earlier generations showing therapeutic efficacy for tendinopathies and joint osteoarthritis. As the field of Orthobiologics continues to rise, early investigators in the field have a responsibility to strive for cohesiveness and standardization in an attempt to provide the highest level of safety and therapeutic efficacy for patients. In order to satisfy this responsibility and progress in the field of Orthobiologics, it is important to establish a common definition of current Orthobiologic options, improve access to continuing education, and facilitate research collaboration throughout the global medical community.

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1. INTRODUCTION

Over the past 10 years, the field of Orthobiologics has grown rapidly and started to establish a foundation as a potentially safe and efficacious alternative for a variety of musculoskeletal injuries, including osteoarthritis and chronic tendinopathies. With life expectancy on the rise, and an aging population of baby boomers, the demand for viable minimally invasive options is at an all time high. The increased demand has led to scores of physicians attempting to integrate regenerative options into their practices. However, as the exponential growth of Orthobiologics continues to skyrocket, coordinated research efforts haven't been able to match the same trajectory, resulting in a paucity of high level of evidence studies. As the volume of physicians utilizing Orthobiologics continues to rise, the burden is bestowed to early investigators in the field to strive for cohesiveness and standardization in an attempt to provide the highest level of safety and therapeutic efficacy for patients. In order to satisfy this responsibility and progress in the field of Orthobiologics, it is important to establish a common definition of current Orthobiologic options, improve access to continuing education, and facilitate research collaboration throughout the global medical community.

Orthobiologic treatments, as they pertain to the musculoskeletal field, are defined as any treatment modality that utilizes cellular components within the body's native cells, and redirects their use towards damaged or diseased tissues[1,2]. They are often concentrated versions of the body's natural occurring fluids, such as blood, bone marrow, or adipose tissue. Most commonly, they are utilized as an injectable treatment for joints, tendons, or ligaments. Most Orthobiologic injections are performed under image guidance, with either musculoskeletal ultrasound (fig. 1) or fluoroscopic guidance[3]. However, arthroscopy may also be utilized to provide high definition color visualization for accurate cellular deployment. Since the birth of the term Orthobiologics, the field has continued to expand underneath this umbrella term, however the core of Orthobiologic treatments can be classified by 4 generations: hyaluronic acid (HA), platelet rich plasma (PRP), bone marrow concentrate (BMC) and adipose derived mesenchymal stem cells (aMSC) or lipoaspirate.

2. HYALURONIC ACID

The first generation of Orthobiologics is considered to be hyaluronic acid (HA), which has been used as an intra articular injectable in the treatment of Osteoarthritis since the late 1990s. Hyaluronic acid is a naturally occurring protein in the body with viscoelastic properties which help to decrease frictional forces within synovial joints[4]. During joint degradation with Osteoarthritis, the natural concentration of HA within synovial fluid decreases and HA distribution shifts toward lower molecular weight variants, which leads to increased wear and tear on the joint[5]. In addition, intraarticular low molecular weight HA has also been associated with increased pain with OA[6]. The goal of intraarticular HA administration has been to restore the native HA concentration to its nonpathological concentration. However, many other theorized therapeutic mechanisms of HA have been postulated including shock absorp-

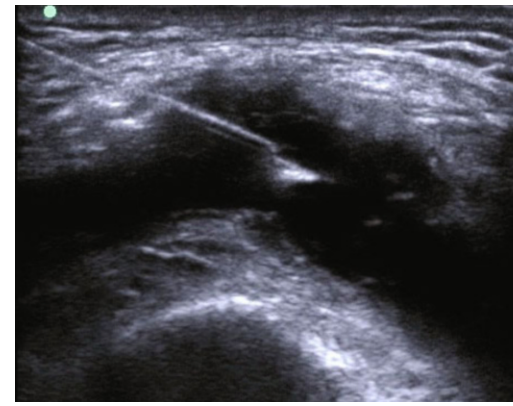

FIG. 1
Right suprapatellar bursae injection under ultrasound guidance.

tion, joint lubrication, anti-inflammatory effects, chrondroprotection, proteoglycan synthesis, and cartilage matrix alterations[5,7]. Although many intrinsic mechanisms have been shown, much of the chrondroprotective and anti-inflammatory mechanisms are correlated with HA binding to cluster of differentiation[44] (CD 44)[8], which inhibits the pro-inflammatory effects of interleukin-1beta, resulting in down regulation of many MMPs associated with cartilage degradation[9].

Although HA is native to intraarticular synovial fluid, the available injectable versions do not currently exist in autologous form, and specific formulations can differ depending on manufacturer and production technique. Some evidence suggests larger molecular weight HA to provide greater anti-inflammatory effects, proteoglycan synthesis, joint lubrication and viscoelastic maintenance compared to lower molecular weight HA counterparts[5]. In addition, avian-derived HA has shown a less favorable safety profile with increased risk for localized intraarticular pseudo septic reactions when compared to HA derived from biological fermentation[10].

The efficacy of intra-articular HA for the treatment of painful symptoms associated with osteoarthritis has been demonstrated in many clinical trials[7], while also providing a superior safety profile when compared to continuous NSAID use for pain control[11-13]. It has also been shown to lengthen the time from diagnosis of OA to time of knee arthroplasty in Medicare (generally senior) patients[14]. Recent OARSI guidelines for the treatment of osteoarthritis suggest "good" level of evidence for the treatment of OA with intraarticular hyaluronic acid[15]. However, previous metaanalyses have illustrated between-study heterogeneity in the efficacy of HA for osteoarthritis, with lower quality studies revealing more efficacious results[16,17], which provides further support for the necessity of high level of evidence studies in the field.

3. PLATELET RICH PLASMA

The second generation of Orthobiologics, platelet rich plasma, was the first autologous Orthobiologic. Although platelet rich plasma (PRP) didn't appear in the sports medicine literature until approximately 2006, it was first used by Ferrari et al in 1987 following open heart surgery[18], and has been used in many other medical fields including ENT, maxillofacial surgery, ophthalmology, urology, dentistry, cosmetic and neurosurgery and wound healing for quite some time. Theoretically, the potent concentration of platelets are injected into soft tissue, tendons, or intraarticularly to stimulate an inflammatory 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. The alpha granules within platelets act as the primary storage center for an array of growth factors including transforming growth factor beta (TGFbeta), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epithelial growth factor (EGF) which are thought to be one of the main reasons for its regenerative potential[19,20]. Newer theories on the mechanism of PRP suggest that intraarticular application may potentially alter the entire joint environment through its effects on the signaling cascade, creating a more advantageous inflammatory environment for healing[21]. Changes in the cellular milieu may potentially exert therapeutic benefits by acting on localized joint tissue cells such as synoviocytes or meniscal cells, promoting chemoattraction of the body's native healing cells to damaged tissue[22,23], or through direct analgesic effect[24]. Although research continues to investigate such theories, the specific mechanism of action for PRP's clinical benefits is unknown. However, the etiology of its therapeutic effects are likely multifactorial and potentially variable across different tissue types.

To date, most of the literature on PRP consists of small case series with mixed results and an underwhelming volume of high-level evidence studies. However, as of late, larger randomized controlled

trials have demonstrated superior efficacy in areas such as chronic tendinopathies[25,26] and knee osteoarthritis[27]. Research has also been published suggesting therapeutic benefits of combining PRP with other Orthobiologic treatments such as HA[28] or MSCs[29,30], as well as utilizing multiple Orthobiologics in a specific sequence as a treatment protocol for Osteoarthritis[31]. Furthermore, protocols have been established for post-PRP recovery and rehabilitative exercises establishing a preliminary framework for doctors and therapists to provide optimal treatment for return to sport[32].

Platelet rich plasma is derived from a patient's venous blood. Blood is drawn from a patient's vein, processed in a centrifuge, and a cellular concentrate, including the buffy coat, which contains the highest concentration of platelets[20], is extracted and used as an injectable treatment (fig. 2). Many researchers have started to emphasize that not all PRP is created equally. Currently, there are multiple cellular processing techniques for extracting PRP. Some practitioners utilize standardized PRP processing kits, which widely differ by manufacturer in regard to cellular composition and delivery methods. While other practitioners perform more individualized techniques, utilizing single and double spin centrifugation cycles and more precise laboratory procedures [32].

As of late, more clinicians are utilizing point of care cellular cytometry to analyze blood products and establish more cellular standardization of injectable PRP (fig. 3). In an attempt to facilitate uniform PRP classification, researchers have established the PLRA PRP classification, which classifies PRP based on the concentration of platelets, leukocyte, red blood cells, and activation technique[33]. Routine classification usage will lead to more customized PRP formulations to maximize therapeutic efficacy for specific musculoskeletal disorders and aide with interpretation of clinical trials. Initial research suggests that leukocyte poor- PRP may have stronger efficacy with intraarticular application[34,35]. As research continues to expand in the area of PRP, the newest generations of Orthobiologics are also beginning to establish a therapeutic framework.

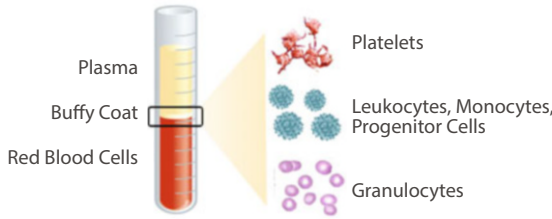

FIG. 2
After venous blood in processed in a centrifuge, it is separated into three layers: Plasma, Buffy coat, and Red blood cells. The buffy coat layer contains the Platelets, which store a variety of potent growth factors, thought to be a primary mechanism of PRP. (Photo courtesy of Ted Sand PhD)

FIG. 3
This is a Cell cytometry analysis of venous blood using the Beckman Coulter ACT 5 DIFF CTL PLUS. This sample is an example of pre-centrifugation data, noted by the normal concentration of platelets. The cytometry data is used to classify PRP based on the PLRA PRP classification system.

4. BONE MARROW CONCENTRATE

Bone Marrow Concentrate (BMC) is considered the 3rd generation of Orthobiologic treatment. 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[36]. 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[36]. Bone Marrow is most commonly aspirated from the posterior iliac crest, utilizing ultrasound or fluoroscopic guidance. The bone marrow aspirate undergoes cellular processing via similar centrifugation mechanisms as platelet rich plasma. Physicians currently have multiple options for marrow concentration, either via standardized manufacturer kits or individualized laboratory techniques, very similar to the PRP options. Similar to PRP, the wide variability with bone marrow aspiration and concentration amongst physicians has added to the ambiguity with standardized treatments and research efforts. As one of the newer generations of Orthobiologics, BMC has a paucity of high-level studies or randomized trials. Although much of the early research has been mixed, some preliminary studies have demonstrated significant patient safety and efficacy with joint Osteoarthritis[31,36-39]. Select practitioners have started to utilize cell cytometry with BMC procedures, similar to the PLRA PRP classification, however no standardized classification exists currently.

5. ADIPOSE DERIVED MESENCHYMAL STEM CELLS (AMSCS)

As the field of Orthobiologics continues to develop, research efforts continue to refine our scientific understanding, opening possibilities for future generations of Orthobiologics. Recent literature has suggested a perivascular origin of MSCs, in the form of pericytes[40], which has led to exploration of other autologous sources of mesenchymal stem cells, including the most recent fourth generation of orthobiologics: Lipoaspirate/ Adipose Derived Mesenchymal Stem Cells (or now termed "Medicinal Signaling Cells.)". Compared with BMC, processed lipoaspirate/adipose-derived MSCs (aMSCs) has advantages, in that it is procured in much larger quantities, and with less invasive techniques under local anesthesia and vacuum-assisted lipectomy. Similar to BMC, processed lipoaspirate has exhibited differentiation into chondro¬genic, osteogenic, adipogenic, myogenic, and neurogenic lineages in the presence of lineage-specific induction factors[41,42]. Although, some research has illustrated that aMSCs actually possess larger numbers of MSCs[40], data is mixed as to whether aMSCs have equivalent osteogenic potential as BMC[43,44]. In addition, aMSCs have been shown to be a more potent immunomodulator compared to bone marrow-derived MSCs, albeit the clinical benefit of such difference has yet to be determined[45]. Preliminary research suggests that aMSCs exhibit an anti-inflammatory effect on chrondrocytes and synoviocytes in patients with Osteoarthritis[46]. In addition, one study examined the combination of BMC with aMSC, although an additive effect was not detected[38].

6. FUTURE GENERATIONS

An emerging allogeneic Orthobiologic option, amniotic tissue, has also been shown to be a source of MSCs[47,48]. However, it does not possess the same resident cell volume as BMC and aMSCs[40]. Few human trials exist for human amniotic membrane applications, but small case studies have shown efficacy for elbow tendinopathy[49] and plantar fasciitis[50], while preliminary animal studies have suggested potentially positive applications for tendon injuries[51] and Osteoarthritis[52]. To date, this source of MSCs is the most under researched and one of the newest on the horizon.

7. FUTURE DIRECTIONS

The field of Orthobiologics is faced with the burden of balancing immense growth and diversification with a firm scientific foundation. And, as the separation widens, the lack of standardization and uniformity amongst practitioners is becoming significantly more apparent. All the more, the field as a whole continues to expand at a paramount rate, risking dilution of the core principles of Orthobiologics, if not matched by coordinated research efforts and continuing education. Currently, there are many national organizations and medical societies that have started to integrate orthobiologics, most noticeably AAOSM, Isokinetics, ICRS, as well as many other spine and orthopedic societies. In addition, educational conferences and workshops are beginning to form, teaching practitioners about emerging treatment options, cellular processing, and injection techniques. However, at the moment, the educational environment for Orthobiologics is disjointed, making it difficult for clinicians to not only stay up to date with emerging research, but also gain the hands-on skills needed to safely execute the treatments in their practices.

Rather than providing small breakout sessions as part of a larger broad-spectrum orthopaedic conference, the most comprehensive events in the field of Orthobiologics provide physicians and surgeons with a one-stop-shop for all things Orthobiologics. Most noticeably, The Orthobiologic Institute (TOBI) has established itself as the premier annual event, focusing solely on PRP, BMC, Lipoaspirate, and emerging areas of Orthobiologics. Starting with its first annual symposium just 8 years ago, and a small group of 25 physicians, the annual meeting has swelled to over 500 attendees, representing more than 30 countries, encompassing physicians and surgeons from a myriad of synergistic specialties. The TOBI annual symposium not only provides the most up to date research, but also offers world-class hands-on training at one of the largest cadaver labs in the world, taught by leaders in the field.

In the future, conferences and national organizations that provide continuing education in the field of Orthobiologics may potentially collaborate to form a board certification or certificate of competency for such specialties. Although most physicians are learning Orthobiologic principles after residency training through conferences and workshops, it is likely that the younger generation of physicians will start to gain earlier exposure to Orthobiologics in certain medical specialties such as Physical Medicine and Rehabilitation, Pain Management, Sports Medicine, or Orthopaedic Surgery. In addition, numerous non-accredited fellowship opportunities have started to form as of late, providing new residency graduates with more specialty training underneath an Orthobiologic mentor.

Because of the extensive treatment diversity across the industry, future research efforts for Orthobiologics will incorporate international data registry software to monitor patient outcomes, track patient safety, and analyze cellular compositions for biologic formulations. Recently, a not for profit foundation, the Regenerative Orthobiologics Registry, was started by the coauthors of

this chapter to provide a framework for collecting patient data to elevate the field as a whole and improve the safety and quality of Orthobiologic treatments. Larger amounts of PRP, BMC, and Lipoaspirate data will allow for improved efficacy and standardization of treatments, with higher power research studies and more treatment specificity. It is also possible that predictive analytics and integrating Precision Medicine, a medical model that proposes customization of healthcare to each individual, may help guide research efforts and formulate treatment protocols in the future.

As a whole, the field of Orthobiologics is far from where it started. Although, even with some two decades worth of expansion and scientific discovery, the four distinct generations of Orthobiologics lack a true definition as to what they are, and how they should be used. As of now, we can confidently state that hyaluronic acid, platelet rich plasma, bone marrow concentrate, and adipose tissue have established a place for themselves in the future of Orthobiologics. However, investigation into their therapeutic applications, optimal cellular compositions, and treatment protocols lag behind their widespread use. With more commercial biologic options rapidly surfacing, it behooves the industry to establish a proper framework for preexisting biologic options, before moving onto to newer injectables. As the current state of Orthobiologics would have it, the burden lies with the physician to increase their education through annual conferences, such as The Orthobiologic Institute (TOBI), and pursue more collaborative research efforts. Although we cannot predict where the field will be in another 10 years time, by establishing more opportunities for physician education and coordinated research, we can help increase Orthobiologic's credibility and insure its longevity as a minimally invasive tool to combat musculoskeletal disease.

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